

NEW AND NONOFFICIAL REMEDIES, 1946

Containing Descriptions of the

Articles Which Stand Accepted by the Council
on Pharmacy and Chemistry of the
American Medical Association
on January 1, 1946

Under the Direction and Supervision of the Council on
Pharmacy and Chemistry of the American
Medical Association

Approved by the Council on
Pharmacy and Chemistry of the American
Medical Association

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PREFACE

This book is published by the Council on Pharmacy and Chemistry, which is a standing committee appointed by the Board of Trustees of the American Medical Association to consider medicinal preparations offered by pharmaceutical manufacturers for prophylactic or therapeutic use by the physician. In it are listed and described articles which the Council has found acceptable up to January 1 of the year of publication. It is thus a cumulative epitome of agents which the Council has found acceptable since it was first established in 1905. The book is constantly in review by the Council to eliminate preparations which have not lived up to their promise of value. Each year the general articles on the various classifications of preparations are reviewed to bring them up to date with current medical

interest to the medical profession.

The descriptions of accepted articles contained in this book are based in part on investigations made by, or under the direction of the Council and in part on evidence or information supplied by the manufacturer or his agents. Statements made by those commercially interested are examined critically and admitted only when they are supported by other evidence or when they conform to known facts.

While it is not the normal procedure of the Council to consider pharmacopœial drugs, such preparations have been included under special circumstances as explained in the Council's rules. A number of such articles are listed in the present volume. The Council recently decided to cease consideration of those official preparations, the actions, uses and nature of which are so well understood by physicians as not to require their inclusion in New and Nonofficial Remedies. Brands of the following have thus far been thus exempted from consideration:

Iron and Ammonium Citrates
Ferrous Sulfate
Calcium Gluconate
Antimeningococcic Serum
Liver and Stomach Preparations included in U S P
Dig talis Preparations included in U S P
Acetylsalicylic Acid
Caffeine with Sodium Benzoate
Carbon Dioxide
Oxygen
Oxygen Carbon Dioxide Mixtures

Chlorinated Paraffin (Chlorocerosane)
 Cinchophen
 Neocinchophen
 Dextrose Solution
 Sodium Chloride Solution
 Isotonic Solution of Three Chlorides
 Sodium Citrate
 Sodium Diphosphate
 Magnesium Sulfate
 Trioxymethylene (Paraformaldehyde U S P X)
 Methylene Blue
 Quinine and Urea Hydrochloride
 Salicylic Acid
 Sodium Salicylate
 Natural Oil of Sweet Birch (Methyl Salicylate)
 Pentobarbital Sodium
 Papaverine Hydrochloride
 Emetine Hydrochloride
 Totaquine
 Tribasic Calcium Phosphate
 Magnesium Trisilicate
 Tribasic Magnesium Phosphate
 Ichthammol Preparations
 Strophanthin

Solutions referred to in the descriptions of qualitative and quantitative tests are unless otherwise stated of the strength described in the U S Pharmacopeia or the latest supplement in effect at the time of printing New and Nonofficial Remedies. Unless otherwise specified, percentage statements, in general, refer to weight over weight.

During the year 1946 descriptions of such other medicinal substances as are accepted by the Council for N N R will be published from time to time in *The Journal A M A* and will be reprinted in the form of a supplement which will be sent to those who purchase this book.

In line with action taken by the Council during 1943, only the metric system will be used henceforth in the publications for which the Council is responsible. Adequate conversion tables may be found in each publication for those who wish to convert other units into metric equivalents.

Acknowledgement is made of the continued assistance of Cecil Bean, M A, Anne Shumkus and Diana Korkoneas of the Council office, and of Albert E. Sidwell, Ph D, Director of the A M A Chemical Laboratory. Criticism of physicians and pharmaceutical manufacturers is invited with a view to any further improvements of the book.

AUSTIN SMITH, *Editor*

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Annand P N	Washington D C
Binkley George W M D	Cleveland Ohio
Borts I H M D	Iowa City Iowa
Cook F Fullerton M D	Philadelphia Pa
Crossen Robert J M D	St Louis Mo.
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DeCralf Arthur C M D	New York N Y
Deweese A Lovett M D	Arli ore Ia
Eastman Nelson J M D	Balti ore Md
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Hanzlik P J M D	San Francisco Calif
Hinslaw H Corin M D	Rochester Minn
Hodges Paul C M D	Chicago, Ill
Hopkins Joseph C M D	New York N Y
Ivy A C M D	Chicago Ill
Ielmann Robert M D	New York N Y
Ievy Robert M D	New York N Y
Iew s George M M D	New York N Y
Indsay J R M D	Chicago Ill
Luddy John M D	Pocheater Minn
Mallmann W L M D	East Lansing Mich
Morton H E Sc D	Philadelphia Pa
Neal Paul A M D	Bethesda Md
Powers J st n I Ph D	Walto D C
Qu n by Ed th M D	New York N Y
Rose Wm C M D	Urbana Ill
Rotlman S M D	Chicago Ill
Stevens Franklin A Jr M D	New York N Y
Strker Cecil M D	Cincinnati Ohio
Van Winkle Walton Jr M D	Washington D C
Veldee M V M D	Bethesda Md
Wallace Donald Ph D	Chicago Ill
We dman Fred D M D	Philadelphia Pa.
Wilder Russell M M D	Locheester Minn

the case of mixtures description of methods for determining the amount and strength of the potent ingredients shall be furnished, if practicable

Rule 3—DIRECT ADVERTISING—No article that is advertised to the public will be accepted or retained, but this rule shall not apply to (a) disinfectants germicides and antiseptics provided the advertising is limited to conservative recommendations for their use as prophylactic applications to superficial cuts and abrasions of the skin and to the mucous surfaces of the mouth pharynx and nose (but not to those of the eye and the gastrointestinal and genitourinary tracts) and provided they are not advertised as curative agents (see comments to Rule 3), (b) liquid petrolatum and simple preparations of liquid petrolatum agar and simple preparations of agar, and similar preparations which act because of their bulk provided that such lay advertising carries a warning that agar and similar preparations may be harmful in colitis (c) other agents about which the public should be informed and which would not lead to harmful self medication provided (1) that they are not advertised as curative agents and provided (2) that the advertising to the public does not go beyond that passed by the Council for physicians (Rule 6)

Rule 4—INDIRECT ADVERTISING—No article will be accepted or retained if the label package or circular accompanying the package contains the names of diseases in the treatment of which the article is said to be indicated. The therapeutic indications and properties may be stated provided such treatments do not suggest self medication. This rule shall not apply to remedies altogether improbable to vaccinations for administering or as immediate heroic treatment is . . .

Rule 5—FALSE CLAIMS AS TO ORIGIN—No article will be accepted or retained concerning which the manufacturer or his agents make false or misleading statements as to source raw material from which made or method of collection or preparation

Rule 6—UNWARRANTED THERAPEUTIC CLAIMS—No article will be accepted or retained concerning which the manufacturer or his agents make unwarranted exaggerated or misleading statements as to the therapeutic value. Therapeutic representations made in the labeling advertising etc must be confined to those given in N N R or otherwise accepted by the Council

Rule 7—POISONOUS SUBSTANCES—The principal label on an article containing poisonous or potent substances must state plainly the amount of each of such ingredients in a given quantity of the product

Rule 8—OBJECTIONABLE NAMES—Proprietary names for medicinal articles will be recognized only when the Council shall deem the use of such exclusive names to be in the interest

of public welfare. Names which are misleading or which suggest diseases, pathologic conditions or therapeutic indications will not be recognized (the provision against therapeutically suggestive names does not apply to serums, vaccines and antitoxins). In the case of pharmaceutical preparations or mixtures the name must be so framed as to indicate clearly the most potent ingredients. Coined names for salts will not be accepted unless such names indicate the components of the salt, coined names for new substances marketed as pharmaceutical preparations will not be accepted unless such names indicate definitely the type or dosage form of the article.

Rule 9—PATENTED PRODUCTS AND PROTECTED NAMES—If the article is patented—either process or product, or both—the number of such patent or patents must be furnished to the Council. Furthermore, if the name of an article is registered or the label copyrighted the registration (trademark) number and a copy of the protected label should be furnished the Council. In case of registration in foreign countries the name under which the article is registered should be supplied. This information is important as a means of determining the legal status of medicinal articles and an aid to their ready recognition in current publications.

Rule 10—UNSCIENTIFIC AND USELESS ARTICLES—No article will be accepted or retained which, because of its unscientific composition is useless or inimical to the best interests of the public or of the medical profession. This class includes compounds or mixtures containing an excessive number of active ingredients, those compounds or mixtures the components of which are of no probable assistance to one another, those articles which are of no therapeutic value and those which carry with their administration an unwarranted danger.

Rule II—POLICIES OF FIRMS DETRIMENTAL TO RATIONAL THERAPEUTICS—The Council will not accept or retain, if already accepted the articles of a firm if in the opinion of the Council the policies of such a firm are clearly detrimental to the welfare of the public and to medicine.

EXPLANATORY COMMENTS ON THE RULES

PURPOSE AND METHODS OF THE COUNCIL.—The Council on Pharmacy and Chemistry was established in 1905 by the American Medical Association. The Council examines articles on the market as to their compliance with definite rules and describes their essential features in New and Nonofficial Remedies (N. N. R.).

Submit^{ed} evidence—These departments are required to report on investigations but in part the "evidence" is the "evidence" of the manufacturers and the "evidence" of the manufacturers is the "evidence" of the manufacturers.

every complex pharmaceutical mixture or to check thoroughly every therapeutic claim, it can give only unbiased judgment on the available evidence. Criticisms and corrections of the descriptions which may aid in the revision of the matter will be appreciated.

Previous Noncompliance and Fraud—The Council judges an article entirely by the facts in evidence at the time of its admission. Previous noncompliance with the rules (short of intentional fraud) does not prevent the favorable consideration of an article which is in accord with existing rules. Infractions of the rules after acceptance of an article for New and Nonofficial Remedies, or the discovery that the Council's information was incorrect, will cause the acceptance to be reconsidered.

Reconsideration—An article is accepted for New and Nonofficial Remedies and will continue to be included in the book subject to examination every three years or more frequently if indicated with the understanding that serious violations of the rules after acceptance will be followed by the omission of the article and publication of the reasons for such omission.

Acceptance Not an Indorsement—The Council desires physicians to understand that the admission of an article does not imply a recommendation. Acceptance simply means that no conflict with the rules has been found by the Council.

Seal of Acceptance—For articles which are accepted for inclusion in New and Nonofficial Remedies the Council permits the use of its official seal of acceptance with the following stipulations: (1) The seal may be used on the packages of an article and in the advertising for it. (2) The seal is used and is the only seal of such character to appear. No objection is made, however, to any statement or device required or permitted by the government in securing compliance with regulations of a government bureau or department. (3) If the seal is used in price lists and catalogs which also feature unaccepted articles, it must be used for accepted articles in such a manner that there can be no implication that the seal applies to the unaccepted articles. (4) The following statement in reference to the significance of the seal may be used in connection with the seal: The accepted seal denotes that [name of article] has been accepted for New and Nonofficial Remedies by the Council on Pharmacy and Chemistry of the American Medical Association. Further statements in regard to the seal must be submitted to the Council and be found acceptable before they may be used. (5) The size of the seal on the package shall not be greater than one inch in height or diameter, and in advertising it shall be in proportion to the dimensions of the advertisement so as to afford ready recognition, but undue size giving greater prominence to the seal than to other important features of the advertisement or detracting from the dignity of the seal in the opinion of the Council will not be permitted. (6) When for any reason the acceptance of an article is rescinded the seal

must not appear on new labels or in new advertising for such article, and old labels and advertising which feature the seal must not be in circulation, in evidence, or before the public longer than six months subsequent to notification of the revocation.

Duration of Acceptance—Unless otherwise determined at the time of acceptance, articles admitted to New and Nonofficial Remedies will be retained for a period of three years, provided that during that period they comply with the rules and regulations which were in force at the time of their acceptance. New evidence indicating that compliance with the rules no longer exists, for instance, with regard to unwarranted therapeutic claims, will be considered the basis for reconsidering the acceptance before the end of a period of three years. At the end of this period, all articles will be carefully reexamined for compliance with existing rules. Particular weight will be given to the question as to whether recent evidence has substantiated claims as to the therapeutic value of any preparation; this evidence to consist partly of recent statements in the literature and partly of the general esteem in which the preparation is held by clinical consultants of the Council. The reacceptance of articles after such reexamination shall be for three years unless a shorter period is specified.

Any amendments to the rules, by specific requirements or by interpretation which may be made after the acceptance of an article, shall not apply to such article until the period of acceptance has elapsed. At the end of this period the article if it is not eligible under the amended rules, will be omitted.

The Scope of New and Nonofficial Remedies—To aid physicians and manufacturers in deciding which articles come within the scope of this book, or, in other words, to enable

ing more detailed definitions

Official Articles—Articles official in the U S P, or N F, are exempted from consideration if they are marketed under a name which is generally familiar and which may be taken in such use.

These do not require consideration by the Council since standards for them are provided in these books.

If a U S P or N F product is offered for sale under a name which does not make its official status evident or if the proprietors or their agents advance claims that the product possesses therapeutic properties other than those properly and commonly accredited to it, it becomes subject to consideration by the Council.

Simple preparations or mixtures of official articles may be considered to have the status of official articles if they are marketed under descriptive, nonproprietary names and if unestablished claims are not made for them. At the request of the distributors of such products the Council will determine whether they meet these provisions.

No product which has been official for more than twenty years except preparations licensable under the Serums, Virus and Vaccine Act, will be considered for inclusion or retention in New and Nonofficial Remedies. All preparations which are licensable under the Serums, Virus and Vaccine Act including arsenicals for the treatment of syphilis, are eligible for consideration for inclusion or retention in New and Nonofficial Remedies, regardless of their official status.

Modifications of U S P and N F Products—A Pharmacopoeial or National Formulary product which is marketed under the official title or synonym, but with well founded claims that its purity, permanence, palatability or other physical properties excel the official standard may, if no extraordinary therapeutic properties are asserted, be considered as an official article and held not to be within the scope of New and Non official Remedies.

When such products are marketed under the claim that they possess therapeutic properties other than those commonly accredited to the U S P or N F products of which they are modifications they become subject to the consideration of the Council.

The burden of proof in establishing claims for therapeutic properties of products considered by the Council shall lie with the proprietor or in the case of a foreign made product with the agent who markets the product in the United States.

Substances Described in New and Nonofficial Remedies.—In the book will be described proprietary pharmaceutical and drug substances if they have originality or other important qualities which in the judgment of the Council entitle them to such place official preparations concerning which the Council deems the medical profession not yet fully informed, or any other article, the inclusion of which is believed to give useful information to the physician. An article will not be accepted or retained unless it is found in the open market under the name of the firm under which it is submitted or accepted. The term 'open market' contemplates both the wholesale and retail merchandising of drugs.

Proprietary Mixtures—A mixture will be considered as proprietary, and therefore requiring consideration by the Council for admission to the book if it contains any proprietary articles, if it is marketed under a name which is in any way protected or if its manufacturer claims for it any unusual therapeutic qualities.

Wiederum ist $H^0(\mathcal{O}_X) = \mathbb{C}$. Nach dem Satz von Serre über die Kohomologie kohärenter Garben gilt also

It is not surprising that the results of the present study are in line with the findings of other studies. For example, the results of the present study are in line with the findings of the study by Kline and Kline (2002) who found that the use of a single-item measure for a construct is acceptable if the item is a good representation of the construct. The results of the present study are also in line with the findings of the study by Nunnally (1978) who found that a single-item measure is acceptable if the item is a good representation of the construct. The results of the present study are also in line with the findings of the study by Cronbach (1951) who found that a single-item measure is acceptable if the item is a good representation of the construct.

[illegible][illegible]

1. 在 1949 年 10 月 1 日以前，凡在中华人民共和国领域内，
 2. 有犯罪行为，或者具有下列情形之一的，均适用本法：(一)
 3. 在中华人民共和国领域内犯罪的；(二)在中华人民共和国领域
 4. 外犯罪，依照本法规定应当受刑罚的；(三)在中华人民共和国
 5. 领域外犯罪，依照本法规定应当受刑罚，但是按照犯罪地的法
 6. 律不受刑罚的；(四)在中华人民共和国领域外犯罪，依照本法
 7. 规定应当受刑罚，但是按照犯罪地的法律不受刑罚，而按照
 8. 本法规定应当受刑罚的；(五)在中华人民共和国领域外犯罪，
 9. 依照本法规定应当受刑罚，但是按照犯罪地的法律不受刑罚，
 10. 而按照本法规定应当受刑罚，且按照本法规定应当受刑罚的。

[illegible]

that is impracticable on the carton label or individual package insert in the event that no preservative is present the absence must be declared. The definition of 'preservative' is intended to include all substances used for the purpose of preserving the identity, strength, quality or purity of a preparation. Thus not only bactericidal or bacteriostatic agents are required to be declared in the labeling but other chemicals such as stabilizers, antioxidants and buffers.

Preparations containing 1 per cent or more of benzyl alcohol must have this ingredient included as part of the name inasmuch as benzyl alcohol in such amounts acts as a local anesthetic and would constitute a potent therapeutic agent. For example, solution sodium morrhuate 5% with benzyl alcohol 2%.

The Council requires that chlorobutanol be included in the title of those preparations which contain more than 0.5 per cent of chlorobutanol unless the manufacturer can show evidence that the presence of this amount does not have therapeutic as well as antiseptic effect.

Trade Secrets—Furthermore trade secrets will not be received as confidential by the Council since it accepts information only with the distinct understanding that this may be freely published at its discretion.

Inspection of Factories—The Council does not routinely accept invitations to inspect factories; its concern is with the finished products. If such action seems indicated a representative may visit the factory or principal place of business and manufacture to obtain first hand information concerning the nature of the manufacturing establishment, the facilities and controls available and the nature of the laboratory and experimental facilities operating in conjunction with the plant and for authenticating representations concerning scientific personnel and investigative projects.

Nonofficial Constituents—Nonofficial constituents of proprietary mixtures must be presented by the manufacturer in the regular way and must be acted on by the Council before the preparations containing them can be accepted. Constituents that are not concerned in the pharmacologic action of the preparation need not be submitted in detail but their nature and quantity must be disclosed to the Council so that it may be judged that they are inert. They must be declared on the label or package by such designations as will make their nature apparent.

Deliberate Misrepresentation—When it appears that a manufacturer has made a *deliberately* false statement concerning a product he is asked to furnish an explanation and if this is not satisfactory the product will not be accepted even if the false statement is subsequently corrected or omitted.

Testimonials—The foregoing paragraph applies not only to statements made to the Council but also to statements furnished to physicians by the manufacturer or his agents even when these statements are in the guise of testimonials.

Rule 2—Identification.—In order to avoid errors in the case of chemical compounds and to guard against a temporary lack of potency or strength and the possibility of one chemical for another, it is necessary to have at least a visible test.

Tests, etc.—If these facts have appeared in the literature or in standard textbooks reference to them will be sufficient with new chemicals, especially synthetic, the manufacturer or his representatives will be required to supply such tests for purification as well as to arrange for a comparison of these products.

Physico-chemical Standardization.—In cases in which chemical methods of identification are unknown or unreliable physico-chemical standardization should be employed. The Council considers the phrase "physico-chemically standardized" or "assayed as prescribed" covers the standard and method are published in sufficient detail to permit of their control by independent investigation.

It is evident that when no standard is published it is impossible to know whether the quality is high or low and it is impossible to learn without actual trial the relative value of one preparation as compared with that of another manufacturer or to confirm or disprove the statements of the manufacturer as to the quality of his product.

Rule 3—Direct Advertising to the Public.—The importance of controlling the irresponsible claims in advertisements to the public is well known and one of our chief duties is to bring to the attention of the public that they are suffering from the many diseases described the dangers of the remedies and the serious nature of a drug habit and the evils of harmful self-medication is holding the dangers of the spread of many infectious and contagious diseases when ill from the physician are the reasons for discouraging in the interest and for the safety of the public this form of exploitation. Advertising in medical journals and other publications distributed solely to physicians, or in journals for dentists pharmacists nurses and veterinarians does not come within the scope of this rule provided such advertising does not invite or encourage use by unqualified persons.

Exceptions.—In the case of subjects on which the public should be instructed as in the use of certain disinfectants germicides, antiseptics laxatives and such other articles as the Council may specify, advertisements to the public if not in objectionable forms are considered admissible. In no case shall such advertisements include recommendations for use as curative agents nor shall the names of any disease appear on or in the trade package except in connection with prophylactic recommendations. If the preparation is sufficiently toxic to require caution in its use to prevent poisoning this fact shall be stated on the label.

Advertisements in Foreign Countries—The Council in determining the status of any article must take into consideration any statements made regarding it or any method of advertising it employed by the manufacturer or his authorized agents or representatives whether in this country or abroad. No objection will be raised to the use of a statement such as 'This substance is accepted by the Council on Pharmacy and Chemistry of the American Medical Association under the name of ' when such a statement is used in the promotion of a Council-accepted preparation sold outside of the United States under another name, provided the firm makes no misleading claims and meets the other rules of the Council, otherwise Council acceptance may be compromised if violation of the rules comes to the attention of the Council.

The Council does not regard as within its scope the acceptance of articles marketed solely outside the United States.

Rule 4—INDIRECT ADVERTISING TO THE PUBLIC—This rule imposes no restriction on the legitimate methods of bringing a remedy to the attention of the profession such as advertising in medical journals, circulars and other printed matter distributed solely to physicians. The rule applies only to the package as it may reach the patient.

Naming Diseases on Label—The naming of diseases on the label or package is not necessary, as is shown by the very large number of proprietary products which have been successfully introduced without resorting to this expedient.

Therapeutic Indications—In general, therapeutic indications should be omitted from the label and package. The Council will not insist on this point, however, when such indications are so given as not to promote self-medication, particularly in diseases which require expert diagnosis and supervision.

Permanently Affixed Names—It will be considered an infringement of the rule if an article is marketed in bottles which have the name of the article blown into the glass, or if otherwise the name or initial or other distinctive mark of the article is permanently stamped on the container, on the article itself, or is on the stoppers or seals if the article is one that may be used for self-medication. Articles which are marketed in any of these ways are not accepted for New and Nonofficial Remedies. Readily removable labels, are not objectionable, nor is the permanent affixing of the firm's initials or name to the trade package if such initials or name is not suggestive of the article.

Radio Advertising—The Council is of the opinion that advertising specific medicinal articles over the radio would be analogous to advertising them by newspaper, the effect of both is to advertise to the public and is objectionable. Advertising the name of a firm as being a reliable one is permissible.

Use of Articles for Advertising Unacceptable Articles—The Council does not countenance the use of an accepted article for

advertising other articles which have not been accepted by the Council. The Council therefore objects to the mailing of circulars for accepted and unaccepted articles in one envelop if misleading statements are made in regard to the status of the various preparations under the Council's rules, if there is reason to believe that the method of presentation will tend to mislead the reader, and if it is not made clear beyond doubt which of the products have been accepted by the Council, and which have not been accepted. This clause does not apply to advertising material circulated exclusively to dealers. The Council takes no exception to the use of the abbreviation "N N R" as a means of distinguishing Council accepted articles in those instances where the grouping of accepted and unaccepted products together is deemed likely to be misleading or confusing from the standpoint of their Council status. Nor will the Council accept an article or continue the acceptance of an article if the same article or an essentially similar one is marketed by the same firm under another name which has not been recognized. When, in the opinion of the Council, a firm secures the acceptance of one or more articles and employs the acceptance in a way that promotes the exploitation of articles that are opposed to the principles of the rules of the Council the preparations of the firm will be dismissed summarily and no preparations of that firm will be accepted by the Council.

Rule 5—FALSE CLAIMS AS TO ORIGIN—No false or misleading statement in regard to an article can be permitted concerning the source or material from which it is made or the persons by whom it is made.

Rule 6—UNWARRANTED THERAPEUTIC CLAIMS—This rule insists that the claims of manufacturers or agents concerning the therapeutic properties of their products must be compatible with demonstrable facts. Manufacturers will be held responsible for all statements made or quoted in their advertising "literature" regarding their products. The use of the personal signature of a physician, or the facsimile of such signature on the label, or in advertising of products is objectionable because it tends to create, through the implication of personal supervision, an exaggerated or misleading impression of therapeutic value, and articles so labeled or advertised are therefore not acceptable. Therapeutic claims made subsequent to the acceptance of an article must be submitted to the Council for review provided such claims exceed, or substantially modify those made at the time of acceptance. Recognizing the existence of honest differences of opinion on many therapeutic questions the Council desires to be liberal in the application of this rule. It is natural that a manufacturer should be partial toward his own product, and a moderate degree of emphasis in advertising may not be objectionable. The Council however, will

not admit claims which are neither in harmony with already accepted facts nor supported by acceptable evidence. In passing on advertising material, the Council endeavors to indicate the type of claims which are acceptable and the nature of objectionable statements. It is not a function of the Council to edit advertising copy word for word and sentence for sentence but rather to indicate the general type of revision required in any given piece of advertising copy. The Council holds the firm responsible for compliance with the specifications of the Council's objections and expects the spirit and intent of such objections to be observed in the remainder of the copy not specifically criticized. Advertising copy which has been accepted by the Council may be used in whole or in part in later advertising without further submission for examination provided that this does not exceed the scope content and purpose of the original material and provided that there have not been any developments which would invalidate the original material. In doubtful cases the Council considers these questions with the advice and cooperation of its staff of clinical consultants.

Therapeutic claims that do not exceed the statements in the current New and Nonofficial Remedies will not be challenged as a rule, but if the Council finds reason to doubt the validity of any description in New and Nonofficial Remedies, it may require the manufacturer to submit further evidence if he desires to continue such claims.

As new pieces of advertising copy are prepared they should be made available for Council examination or Council files depending on the status of the claims involved. Since the claims of the manufacturer are judged largely by their advertising noncompliance of the manufacturers with the Council's request for copies of the current advertising may be sufficient ground for the rejection of an article unless in individual cases the Council deems such submission unnecessary.

The Council holds that the terms advertising and advertising literature include films and similar devices for informing the public or the profession.

Clinical Evidence—To be acceptable, the clinical evidence must offer objective data with such citation of authority as will enable the Council to confirm the facts and establish the scientific value of the conclusions drawn. The amount and character of the evidence which is required depends on the inherent probability of the claims. No evidence is needed for a self evident claim, very strong evidence is needed when the claim is contrary to the accepted data of science. The acceptability of evidence is determined mainly by its quality. The mere multiplication of inaccurate observations does not render them accurate. The evidence must be furnished in sufficient detail to permit judgment as to the care with which it was gathered.

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permit verification are subject to suspicion. The credibility of the data and the justification of the deductions is influenced by the reputation and experience of the investigators as to disinterestedness, technical ability and critical sense. Anonymous communications and observations gathered without adequate facilities are usually worthless as evidence.

References to Medical Literature—References to medical literature in advertising for an accepted product should be accompanied by the name of the investigator and the year of publication or by full reference to the publication to which reference is made.

Rule 7—POISONOUS SUBSTANCES—All articles containing such potent drugs as the poisonous alkaloids and other organic substances and the salts of some of the metals should have the exact amount of these ingredients which is contained in the average adult dose stated on the label.

NOTE—The Council wishes it understood that any claims of nontoxicity that are made for drugs that have or are supposed to have important general effects are admitted to this book only when they do not conflict with known facts. In all such instances, however, it is recommended that a claim of lack of toxicity be not accepted too freely, but be considered to mean only that toxic effects have not as yet been recognized with the doses that have been studied. The most sincere and apparently justified beliefs concerning this point are often ultimately reversed by extended experience. Much the same may be said regarding any claims that drugs are nonirritating.

Rule 8—OBJECTIONABLE NAMES—Many of the abuses connected with proprietary medicines arise from coined proprietary trade names.

Proprietary ('Trade') Names When Permitted—In consideration of the benefits which may come from the discovery of a therapeutic agent, the Council concedes to the person or firm which, by right of discovery, controls such a product the right to name it. The Council will offer no opposition to an arbitrary name for such a new product provided it is not misleading, therapeutically suggestive or otherwise subversive of scientific pharmacy and therapeutics.

The burden of proof for establishing and continuing recognition of a proprietary name lies with those who market the product. If the discovery that a previously known substance has therapeutic value is deemed of sufficient importance, the Council may recognize a name for such a substance if the name is applied by the person who makes the discovery, or with the consent of the discoverer or in the absence of any protest on his part the Council may recognize a name applied by the firm which first makes such a product available to physicians. Under these conditions the Council may also recognize proprietary names when new uses

or actions of exceptional novelty and importance are discovered for substances previously used in medicine, but which had become practically obsolete. In the interest of rational drug therapy, the Council recommends that trade names be coined so as to indicate the potent element or constituent.

Since the use of numeral or alphabetical designations in connection with drug names tends to take the emphasis away from the name and to disguise the name, thus leading to confusion, the Council will not recognize the name of a drug in which the numeral or letter is an integral part of the name, except in special cases where the use of a numeral or letter seems desirable because further improvement of the product is anticipated, in which case the Council may grant a special exemption from the rule. Under this rule the use of numerals or letters in connection with the name of a product will not be permitted on labels or in advertising unless the numeral or letter is clearly separated from and subordinated to the name by type, and is feasible by position. This rule shall not apply to price lists and catalogs.

For names of accepted products marketed in foreign countries under different names see comments under Rule 3.

When the proprietary or trade name for an article is considered insufficiently descriptive of its chemical composition or pharmaceutical character, the Council may require as a condition for the acceptance of such articles that a descriptive scientific name satisfactory to the Council appear on the labels, circulars and advertisements for such an article. For all definite chemical substances it is required that the scientific (chemical) name be given prominence on the labels in circulars and in advertisements provided that for those substances for which there are recognized Council or pharmacopoeial names such names shall be used and the scientific (chemical) name need not appear.

Proprietary Names for Unoriginal Articles—Proprietary names will not be recognized for articles which are included in the U. S. Pharmacopoeia or National Formulary or for articles which are already accepted in New and Nonofficial Remedies or for unessential modifications of such articles. Neither will proprietary names be recognized for substances or mixtures which are described in medical or pharmaceutical publications except in connection with fundamentally important discoveries relating to articles the use of which had become practically obsolete.

In the marketing of unoriginal articles the legitimate interests of the producer are fully served by identifying such products by appending the name or initials of the manufacturer or agent or by the use of a general brand mark. No objection will be made by the Council to the use of such brand marks provided that in no case shall such mark be used as a designation for an individual article. Names, initials or brand marks

of manufacturers or agents when used to denote proprietorship shall not be of such character as to cause any misunderstanding or confusion as to their significance

For any product which by reason of the absence or lapse of patent rights or for other reasons is open to manufacture by more than one firm the Council reserves the right to select a common name and to provide standards of identity purity and

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National Formulary, it will be omitted from New and Non-official Remedies one year after such standardization if the name of such article is used in these compendiums as the recognized name of the article and if the medical profession is generally familiar with its uses and with the precautions which should be taken in such use. If the name under which the article is described in New and Nonofficial Remedies is not used in these books of standards the proprietary preparation will be retained if otherwise acceptable, provided the official name is given prominence on the labels and in the circulars and advertisements of such article

When the Council adopts a common name for an article that has been admitted under another name it will be continued under the older name only on condition that the Council name be given prominence on the label and in the circulars and advertisements for such article

Pharmaceutic Preparations and Mixtures—These, with rare exceptions are not original in composition and should not be endowed with uninforming names. It is important that they be so named as to remind the prescriber constantly of their potent ingredients. When in the rare exception a pharmaceutic preparation or mixture is accepted with a coined name on the ground of originality because it presents a distinct improvement over available preparations only the first preparation of this kind which is placed on the market shall be recognized under a coined name (which however must clearly indicate the potent constituent of the preparation)

The Council may also recognize coined names for pharmaceutic preparations or mixtures that were in actual use before the establishment of the Council and that have been used continuously since that time and names for mixtures that were named under the reasonably justified bona fide belief that they were chemical compounds provided that such coined names indicate the potent ingredient or ingredients of the preparation are not misleading and do not suggest diseases pathologic conditions or therapeutic indications

Difficulty frequently arises from the application of coined names to salts. For example a firm introduces the hydro

chloride of a synthetic base under the name "Artificialin." Subsequently the firm decides to introduce the lactate of the same base. If this is called "Artificialin lactate" the name "Artificialin" will now mean the base instead of the hydrochloride which is being marketed under that name. In order to avoid this confusion the Council holds that coined names for salts will not be accepted unless such names indicate the components of such salts, thus "Artificialin hydrochloride", the name "Artificialin," unqualified, is acceptable only for the base.

A similar difficulty may arise when a product is marketed first only as a pharmaceutical preparation to which the manufacturer wishes to apply a short coined name, for example, an elixir of a new hypnotic under the name "Aliphal." If later, the manufacturer elects to market the substance also in powder form an entirely new name would become necessary and this would cause confusion both to the profession and to the trade. The Council therefore holds that coined names for new substances marketed as pharmaceutical preparations will not be accepted unless such names indicate the type or dosage form of the preparation, thus 'Elixir of Aliphal,' "Aliphal Powder," not "Aliphal" unqualified.

For declaration of benzyl alcohol or chlorobutanol in the name of a product, see comments under Rule 1.

Biologicals—A biological product intended for use as diagnostic reagent, vaccine, or as an antibacterial or antitoxic serum should be designated by a name which indicates its biological nature e. g. tuberculin, rabies vaccine, diphtheria toxoid, or diphtheria antitoxin, globulin modified. A proprietary name will be recognized for inclusion in N. N. R. only if the brief offered by the sponsor on behalf of such name meets the Council's rules for nomenclature and the name clearly indicates the nature of the product.

Therapeutically Suggestive Names—Names which carry the suggestion of a therapeutic indication, pathologic condition, disease or organism causing a disease shall be considered therapeutically suggestive. Articles bearing such names will not be accepted for New and Nonofficial Remedies, first, because they are likely to lead physicians into prescribing names instead of remedies, and second, because they tend to encourage unwarranted self-medication by the laity. Even if the name is at first apparently meaningless to the public, its meaning will soon be understood because patients soon learn the technical names applied to their diseases and symptoms.

The prohibition against therapeutically suggestive names is not applied to serums, vaccines and antitoxins, because the accepted nomenclature of the specific organisms used in their preparation makes this unavoidable and because self-medication with them is improbable.

Rule 9—PATENTS, TRADEMARKS, COPYRIGHTS, ETC.—This information is important as a means of determining the legal

status of medicinal articles and as an aid to their ready recognition in current publications

USELESS ARTICLES—The use of modifications of official or is unscientific and serves no purpose. I do not accept products which are therefore must be contrary to the best interests of the medical profession and the public. This class includes compounds or mixtures containing an excessive number of active ingredients, those compounds or mixtures the components of which are of no probable assistance to one another and those articles which are of no therapeutic value.

STANCES—
rights over
introducing
and abuses
Essential
recognition

(The Council interprets the term established nonproprietary product as applying to a preparation of any formula which has been published through any recognized or reasonably accessible channel of publication prior to its appropriation or modification by a manufacturer.) Duplicates of biologic products accepted under the names of the manufacturers will not be accepted under the names of the distributors.

Form for the Presentation of Articles

Any article for inclusion in New and Improved American Medical Association 535 N Dearborn St Chicago. Correspondence with the Secretary should be in duplicate. If only one copy is submitted the firm will be asked for a second copy. Except in special instances the presentation should be accompanied by

(1) A sample of each active ingredient also any other ingredient not described in official compendia or N N R used in preparing the articles.

Three retail packages of the article as it is supplied to the trade. When the identical article is packaged in different quantities not more than three packages of the article need be submitted—for instance where identical lots of tablets are marketed in packages of 25, 100 and 500 the submission of three trade packages of only one of these units is required. However *twenty two copies of the labeling* of each package form should nevertheless be submitted. These should be mounted on paper so that errors through loss from handling may be obviated.

(2) Twenty two copies of *each* advertising circular, pamphlet, booklet, etc. which is used to promote the sale of the product.

Each circular submitted must have plainly stamped on it whether it is for inclusion in a trade package or if it is to be sent *only* to physicians

In the event no promotional material other than labeling is employed a statement to that effect should be made with the understanding and agreement that should advertising or promotional material subsequently be proposed for distribution copies of such material will be submitted to the Council *before it is placed in distribution*

(3) A description in duplicate of the article in general accord with the outline which follows

(4) Protocols of bacteriologic examination signed by a reputable bacteriologist and evidence of clinical usefulness which will present studies on toxicity pharmacology etc for new products (i e not in N N R) involving claims of antiseptic bacteriostatic or germicidal effectiveness or when new claims are advanced Where published papers are available references should be cited Criteria for evaluation of skin disinfectants which the Council deems advisable include

1 Phenol coefficients or other in vitro tests in the absence and in the presence of serum using both vegetative bacterial cells and clostridial spores with suitable recovery mediums containing if known neutralizing substances for the disinfectant being tested

2 Data on germicidal efficiency under conditions simulating actual use by the method of Price (Price P B The Bacteriology of Normal Skin A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleaning *J Infect Dis* 63 301 [Nov Dec] 1938 Ethyl Alcohol as a Germicide *Arch Surg* 38 528 [March] 1939) or better still by an extension of the method of Price (Bernstein L H T Standardization of Skin Disinfectants *J Bacteriol* 43 50 [Jan] 1942) The complications due to possible effects of the germicide on the skin itself should be taken into consideration (Cromwell H W and Leffler Ruth Evaluation of Skin Degerming Agents by a Modification of the Price Method *ibid* p 51)

3 Data on germicidal efficiency by an animal method such for example as suggested by Alice H Kempf and W J Nungester (An In Vivo Test for the Evaluation of Skin Disinfectants *ibid* p 49) or R W Sarber (*ibid* p 50)

4 Evidence from animal experiments regarding irritant action on skin and mucosae and regarding systemic toxicity

5 Critical clinical evidence supporting claims of harmlessness and efficacy

6 Data on the bacteriostatic activity as distinguished from the germicidal activity of the disinfectant

For guidance in reviewing contraceptive products the Council on Pharmacy and Chemistry has proposed the following criteria

FORM FOR PRESENTATION OF ARTICLES 27

1 The use of the word "contraceptive" need not be limited to materials which will prevent conception on every occasion of use

2 Evidence shall be furnished that use of the material decreases the incidence of pregnancy. This evidence may be secured in connection with occlusive devices unless the manufacturer's advertising is directed chiefly toward the use of the jelly or cream without such devices. It is desirable that each case reported should be observed for at least 12 months and that the minimum of 75 patient years of experience should be reported. (Thus 50 patients for 18 months or 25 patients each followed for 3 years would be the equivalent of 75 patients for 12 months.) If cases are excluded from the series on the basis of their being irregular users, the number excluded and the nature of the evidence justifying their exclusion should be stated.

3 Evidence shall be submitted that 100 or more couples have used the material on six or more occasions without subjective injury.

4 Evidence is desirable that 12 or more women have received vaginal applications of the recommended dosage on twenty-one successive days without subjective irritation or injury and without evidence of physical damage shown on speculum examination by a physician with special experience in this field. Inspection of the vagina once a week should be done as a protection to the patient in case the jelly proves to be irritating.

5 The quantitative formula from which the contraceptive mixture is prepared shall seem to the Advisory Committee to be safe and, presumably, effective.

6 The consistency shall be satisfactory to the committee. It shall not show separation into more liquid and more solid portions visible to the naked eye.

7 Evidence shall be submitted that the consistency is not substantially changed after storage for twelve months at 27 C.

8 The consistency shall be reasonably uniform from batch to batch.

9 The spermicidal time of the contraceptive material as measured by the method of Brown and Gamble (Human Fertil. 5:97 [Aug.] 1940) with proportions of material, isotonic solution of sodium chloride and semen of 1:4:5 shall be thirty minutes or less as measured by the average of four or more tests.

10 The use of jellies or creams suggested by the manufacturer need not be limited to use in conjunction with an occlusive device.

11 If a syringe applicator or nozzle is furnished for use in connection with the jelly or cream it shall be sufficiently translucent to permit the detection of air which might lead to inadequate dosage.

12 If a perfume is used a quantitative statement of ingredients is desired

(6) If the product is one not previously admitted to New and Nonofficial Remedies, the manufacturer or responsible agent must present protocols of laboratory and clinical evaluations (toxicity, pharmacology, therapeutics, deterioration etc.) Such protocols should include not only evidence collected by the firm in its own investigations, but references to published papers if available. Twenty-two copies of this material must be provided so that each member of the Council can examine at first hand all submitted evidence. If the material is so exhaustive that twenty-two copies are impracticable, the firm may submit only two copies of all evidence and twenty copies of an unbiased abstract of the evidence, the abstract to be prepared by the manufacturer or distributor. The abstract, in fact the entire presentation could be submitted in mimeographed form.

The "description" is requested to facilitate the work of the Council in determining whether or not an article complies with the rules governing the admission of articles to New and Nonofficial Remedies. To a considerable extent it is used also to prepare the description of the accepted article for the book and for publication in the columns of *The Journal A M A*. It is, therefore, requested that the statements be made exact, clear and concise, and in accord with the following numbered headings. The description should be complete in itself and should not require reference to price lists, catalogs, etc.

1 NAME—The trade name of the article

2 SYNONYMS—Title to be used in prescribing and synonyms if any (See Rule 8)

3 DEFINITION—(a) If the article is a definite substance, its scientific name and its structural chemical formula, so far as can be ascertained (See Rule 1)

(b) If the article is a mixture, a statement of the amount of its active medicinal ingredients in a given quantity, preferably in the percentage form, and in general accord with the statement of quantities as followed in the United States Pharmacopeia. Also the composition of the vehicle and the identity of preservatives if present (See Rule 1)

4 PREPARATION—A general statement of the process of manufacture. The Council does not wish to know the details of manufacturing methods, but only a general outline as an aid in verifying the nature and composition of an article. For ordinary pharmaceutical mixtures the process of preparation is not required. When it is difficult to prove the identity of composition of an article by chemical tests an outline of the manufacturing process may be essential.

5 PROPERTIES—Appearance, odor, taste, etc. If a definite chemical, also the melting point, boiling point, solubility, etc. Important incompatibilities

6. TESTS—(a) If a chemical substance, adequate tests of identity, purity and strength should be furnished including methods of assay. These should be drawn up in the U. S. P. or N. N. R. monograph style. (See Rule 2.) These must include the methods by which the tests are made and the upper and lower limits of the ingredients assayed. For instance, in case of iodides assayed, the amount of iodide found by the method described to be not more than—per cent and not less than—per cent.

(b) If a mixture, a method for the identification and estimation of the chief constituents as desired.

(c) For vitamin preparations which are biologically assayed, protocols signed by a reputable biological chemist should be presented. A statement of the required data for vitamins A and D will be sent on application.

(d) The submission of products intended for injection by any route and those intended for topical application in wounds or body cavities where sterility is of importance, must be accom-

panied by a statement of the results of bacteriologic examination, frequency of examination and any other pertinent advice.

7 PHARMACOLOGIC ACTION—A brief statement of the medicinal properties which the article is claimed to possess and its mode of action where known.

8 THERAPEUTIC INDICATIONS—A brief statement of the conditions and diseases in which the article is claimed to be indicated. (See also statements under (4) and (5) of general discussion.)

9 DOSAGE.

10 HOW SUPPLIED—A list of dosage forms as well as package forms of the product available on the market and a statement indicating whether or not the active ingredient is marketed in bulk.

11 MANUFACTURER—(a) The name of the firm responsible for the finished article.

(b) A statement specifying the identity of the manufacturer of the active ingredients contained in the article.

12 PATENTS AND TRADEMARKS—Number of U. S. patent and number of patent in country of origin. Number of U. S. trademark. If the article is registered in foreign countries the name under which it is registered should be furnished. (See Rule 9.)

If a firm is making its first presentation of an article to the Council, the presentation should be accompanied by a catalog or price list of all the products which the firm sells for human medicinal use, a statement of the laboratory and control personnel of the firm, and a general statement concerning the firm's policies. The Council will not accept or retain if already accepted, the articles of a firm if in the opinion of the Council the policies of such a firm are clearly detrimental to the welfare of the public and to medicine.

Further, the manufacturer or distributor must at this time submit a statement of agreement that it will notify the Council on Pharmacy and Chemistry at once upon the discovery that an error has occurred in the compounding of a Council-accepted drug on the market or upon the discovery that a Council-accepted drug on the market has been found by a governmental agency, the firm itself, or any one else to differ from its standard of identity, strength, quality or purity. This notification shall outline the facts relating to the incident. Failure to fulfill provisions of this agreement in good faith will serve as sufficient cause to give prompt consideration to the acceptance status of the firm.

Table of Metric Doses with Approximate Apothecary Equivalents

The approximate dose equivalents in the following table represent the quantities which would be prescribed under identical conditions by physicians trained respectively in the metric or in the apothecary system of weights and measures.

When prepared dosage forms such as tablets, capsules, pills, etc. are prescribed in the metric system, the pharmacist may dispense the corresponding approximate equivalent in the apothecary system and vice versa. This does not, however, authorize the alternative use of the approximate dose equivalents given below for specific quantities on a prescription which requires compounding, nor in converting a pharmaceutical formula from one system of weights or measures to the other system, for such purposes exact equivalents must be used (see U. S. P. XII Table, page 815).

<i>Weights</i>	
Metric	Approximate Apothecary Equivalents
30 Gm	= 1 ounce
15 Gm	= 4 drachms
10 Gm	= 2½ drachms
7.5 Gm	= 2 drachms
5 Gm	= 90 gr
5 Gm	= 75 gr
4 Gm	= 60 gr (1 drachm)
4 Gm	= 45 gr
2 Gm	= 30 gr (½ drachm)
1 Gm	= 15 gr
0.75 Gm	= 12 gr
0.6 Gm	= 10 gr
0.5 Gm	= 7½ gr
0.4 Gm	= 6 gr
0.3 Gm	= 5 gr
0.25 Gm	= 4 gr
0.2 Gm	= 3 gr
0.15 Gm	= 2½ gr
0.125 Gm	= 2 gr
0.1 Gm	= 1½ gr
0.05 Gm	= ¾ gr
0.03 Gm	= ½ gr
0.02 Gm	= ¼ gr
0.01 Gm	= ⅙ gr
0.005 Gm	= ⅓ gr
0.003 Gm	= ⅓ gr
0.002 Gm	= ⅓ gr
0.001 Gm	= ⅓ gr
0.0005 Gm	= ⅓ gr
0.0003 Gm	= ⅓ gr
0.0002 Gm	= ⅓ gr
0.0001 Gm	= ⅓ gr

If a firm is making its first presentation of an article to the Council the presentation should be accompanied by a catalog or price list of all the products which the firm sells for human medicinal use a statement of the laboratory and control personnel of the firm and a general statement concerning the firm's policies. The Council will not accept or retain if already accepted the articles of a firm if in the opinion of the Council the policies of such a firm are clearly detrimental to the welfare of the public and to medicine.

Further the manufacturer or distributor must at this time submit a statement of agreement that it will notify the Council on Pharmacy and Chemistry at once upon the discovery that an error has occurred in the compounding of a Council accepted drug on the market or upon the discovery that a Council accepted drug on the market has been found by a governmental agency the firm itself or any one else to differ from its standard of identity strength quality or purity. This notification shall outline the facts relating to the incident. Failure to fulfill provisions of this agreement in good faith will serve as sufficient cause to give prompt consideration to the acceptance status of the firm.

The Council on Pharmacy and Chemistry has voted to use exclusively the metric system in any publication for which it has sole responsibility. For this reason a table of equivalents will be provided in each book for those who are familiar only with the apothecary system.

Formerly almost every country had its own system of weights and measures, a practice which resulted in much confusion. The one system which is used almost universally and exclusively in the exact sciences is the metric system, which is based on the decimal system and has for its units the meter and the gram. Other systems still enjoying some popularity, albeit decreasing popularity, are the Apothecaries' or Troy weight, which is used in prescriptions, the Avoirdupois or Imperial Weight, which is used in commerce, and the United States Apothecaries' or Wine Measure, which is not to be confused with the British Imperial System. Examples of the denominations of each system are: Apothecaries—grain, scruple (20 grains), drachm (or dram, 60 grains) Troy ounce (480 grains or 8 drachms), Avoirdupois—grain ounce (437½ grains), pound (16 ounces or 7,000 grains) and the ton (2,000 pounds), Wine Measure—minim, fluidrachm (60 minims), Fluidounce (8 fluidrachms or 480 minims), pint (16 fluidounces), quart (32 fluidounces). For fairly accurate conversion

$$\begin{aligned} 1 \text{ Gm} &= 15.43 \text{ grains} \\ 1 \text{ Gm} &= 0.2572 \text{ dram} \\ 1 \text{ Gm} &= 0.03215 \text{ Troy ounce} \\ 1 \text{ Gm} &= 0.03527 \text{ Avoirdupois ounce} \\ 1 \text{ Gm} &= 0.0022 \text{ Avoirdupois pound} \end{aligned}$$

$$\begin{aligned} 1 \text{ grain} &= 0.0648 \text{ gram (Gm)} \\ 1 \text{ grain} &= 64.8 \text{ milligrams (mg)} \\ 1 \text{ dram} &= 3.888 \text{ grams (Gm)} \end{aligned}$$

$$\begin{aligned} 1 \text{ Troy or Apothecary ounce} &= 31.1 \text{ grams (Gm)} \\ 1 \text{ Avoirdupois ounce} &= 28.35 \text{ grams (Gm)} \\ 1 \text{ Avoirdupois pound} &= 453.6 \text{ grams (Gm)} \end{aligned}$$

$$\begin{aligned} 1 \text{ cubic centimeter} &= 16.23 \text{ minims} \\ 1 \text{ milliliter} &= 16.23 \text{ minims} \\ 1 \text{ milliliter} &= 0.2705 \text{ fluid dram} \\ 1 \text{ milliliter} &= 0.0338 \text{ fluid ounce} \\ 1 \text{ milliliter} &= 0.00211 \text{ pint} \\ 1 \text{ milliliter} &= 0.000264 \text{ gallon} \end{aligned}$$

$$\begin{aligned} 1 \text{ minim} &= 0.06161 \text{ cubic centimeters (cc)} \\ 1 \text{ fluid dram} &= 3.6966 \text{ cubic centimeters (cc)} \\ 1 \text{ fluid ounce} &= 29.57 \text{ cubic centimeters (cc)} \\ 1 \text{ pint} &= 473 \text{ cubic centimeters (cc)} \end{aligned}$$

This degree of exactness, however, is not usually necessary in figuring dosages, and round figures are used in the accompanying tables of approximate equivalents, which will be found more convenient for translating dosages from one system to the other. However, further approximation by the use of household units

Table of Metric Doses with Approximate Apothecary Equivalents—Continued

Weights

Metric	Approximate Apothecary Equivalents
8 mg	= $\frac{1}{8}$ gr
6 mg	= $\frac{1}{10}$ gr
5 mg	= $\frac{1}{12}$ gr
4 mg	= $\frac{1}{15}$ gr
3 mg	= $\frac{1}{20}$ gr
2 mg	= $\frac{1}{50}$ gm
15 mg	= $\frac{1}{10}$ gr
1 mg	= $\frac{1}{60}$ gr
0.8 mg	= $\frac{1}{80}$ gr
0.6 mg	= $\frac{1}{100}$ gr
0.5 mg	= $\frac{1}{120}$ gr
0.4 mg	= $\frac{1}{250}$ gr
0.3 mg	= $\frac{1}{300}$ gr
0.25 mg	= $\frac{1}{400}$ gr
0.2 mg	= $\frac{1}{500}$ gr
0.15 mg	= $\frac{1}{600}$ gr
0.1 mg	= $\frac{1}{1000}$ gr

Liquid Measures

Metric	Approximate Apothecary Equivalents
1000 cc	= 1 qt
750 cc	= $1\frac{1}{2}$ pt
600 cc	= 1 pt
250 cc	= 8 fl oz
200 cc	= 7 fl oz
100 cc	= $3\frac{1}{2}$ fl oz
60 cc	= $1\frac{1}{4}$ fl oz
30 cc	= 1 fl oz
15 cc	= $\frac{1}{2}$ fl oz
10 cc	= $2\frac{1}{4}$ fl drachm
8 cc	= 2 fl drachm
6 cc	=
4 cc	= 1 fl drachm
3 cc	= 45 min
2 cc	= 30 min
1 cc	= 15 min
0.75 cc	= 12 min
0.6 cc	= 10 min
0.5 cc	= 8 min
0.3 cc	= 5 min
0.25 cc	= 4 min
0.2 cc	= 3 min
0.1 cc	= $1\frac{1}{2}$ min

NOTE—A cubic centimeter (cc) is the approximate equivalent of a milliliter (ml)

The Council on Pharmacy and Chemistry has voted to use exclusively the metric system in any publication for which it has sole responsibility. For this reason a table of equivalents will be provided in each book for those who are familiar only with the apothecary system.

Formerly almost every country had its own system of weights and measures, a practice which resulted in much confusion. The one system which is used almost universally and exclusively in the exact sciences is the metric system, which is based on the decimal system and has for its units the meter and the gram. Other systems still enjoying some popularity, albeit decreasing popularity, are the Apothecaries' or Troy weight which is used in prescriptions, the Avoirdupois or Imperial Weight, which is used in commerce, and the United States Apothecaries' or Wine Measure, which is not to be confused with the British Imperial System. Examples of the denominations of each system are: Apothecaries—grain, scruple (20 grains), drachm (or dram, 60 grains), Troy ounce (480 grains or 8 drachms), Avoirdupois—grain, ounce (437½ grains), pound (16 ounces or 7,000 grains) and the ton (2,000 pounds), Wine Measure—minim, fluidrachm (60 minims), Fluidounce (8 fluidrachms or 480 minims), pint (16 fluidounces), quart (32 fluidounces). For fairly accurate conversion

1 Gm = 15.43 grains
1 Gm = 0.2572 dram
1 Gm = 0.03215 Troy ounce
1 Gm = 0.03527 Avoirdupois ounce
1 Gm = 0.0022 Avoirdupois pound

1 grain = 0.0648 gram (Gm)
1 grain = 64.8 milligrams (mg)
1 dram = 3.888 grams (Gm)

1 Troy or Apothecary ounce = 31.1 grams (Gm)
1 Avoirdupois ounce = 28.35 grams (Gm)
1 Avoirdupois pound = 453.6 grams (Gm)

1 cubic centimeter = 16.23 minims
1 milliliter = 16.23 minims
1 milliliter = 0.2705 fluid dram
1 milliliter = 0.0338 fluid ounce
1 milliliter = 0.00211 pint
1 milliliter = 0.000264 gallon

1 minim = 0.06161 cubic centimeters (cc)
1 fluid dram = 3.6966 cubic centimeters (cc)
1 fluid ounce = 29.57 cubic centimeters (cc)
1 pint = 473 cubic centimeters (cc)

This degree of exactness, however, is not usually necessary in figuring dosages, and round figures are used in the accompanying tables of approximate equivalents, which will be found more convenient for translating dosages from one system to the other. However, further approximation by the use of household units

NEW AND NONOFFICIAL REMEDIES

CHAPTER I

ALLERGENIC PREPARATIONS

Allergenic preparations are extracts or solutions of various

fibers used in clothing or in upholstery from plants and from a variety of other substances to which patients may become sensitive. I source for animal bu and of othe their use has appeared rational

Allergenic preparations may be divided into two classes (a) those that produce a reaction when applied to the surface of the skin or mucous membranes (b) those which ordinarily give rise to reaction when introduced internally. Sensitivity to substances in class (a) may often be determined by means of the so-called patch test. Sensitivity to substances in class (b) may often be determined by the so called scratch test or by intra dermal administration.

Solutions of allergens may deteriorate with age so it is necessary that they be used before the expiration of a given time determined by the regulations of the Federal Security Agency and must be stored at a low temperature. To insure sterility the council requires that liquid extracts shall be prepared so as to avoid contamination and that their sale shall be authorized by the Federal Security Agency under the law governing the sale of biologic products. The council requires that the identity of any preservative used in accepted allergic preparations be declared on the label.

Actions and Uses—Allergenic preparations may be used for prophylaxis in instances of hay fever or pollen asthma by employing a series of suitably graded doses of specific pollen extracts up to and through the hay fever season or for the

Dosage—No uniform method of standardization has been adopted. Two methods are acceptable, first standardization by the nitrogen content of the extract, and second standardization by amount of pollen or protein in the extract. The sensitivity of various patients is extremely variable so that the tolerance varies widely. For treatment graduated series of doses are supplied by the manufacturer. Most patients tolerate these standardized graduated doses, but in order to avoid untoward reactions at the beginning of the series, 0.02 cc of the weakest solution should be injected intracutaneously before the series is begun. There should be no reaction or only a minimal wheal following this test.

Bacterial Extracts

THE ARLINGTON CHEMICAL COMPANY

Protein Extracts The following protein preparations are marketed in packages of four 5 cc vials one each of four concentrations. In the case of food and incidental extracts these are 1:10,000, 1:5,000, 1:1,000 and 1:500. In the case of animal epidermal and fur protein extracts the concentrations are 1:100,000, 1:10,000, 1:1,000 and 1:500. Concentrations of 1:500 and 1:100 and occasionally intermediate dilutions are also marketed in 5 and 10 cc vials.

For determining patient hypersensitivity by means of the skin test bacterial protein extracts Arlington are supplied in vials containing 25 mg of powdered material.

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Food, Epidermal and Miscellaneous Extracts

THE ARLINGTON CHEMICAL COMPANY

Protein Extracts The following protein extracts are marketed in packages of four 5 cc vials one each of four concentrations. In the case of food and incidental extracts these are 1:10,000, 1:5,000, 1:1,000 and 1:500. In the case of animal

epidermal and fur protein extracts the concentrations are 1:100,000, 1:10,000, 1:1,000 and 1:500. Concentrations of 1:500 and 1:100 and occasionally intermediate dilutions are also marketed in 5 and 10 cc vials.

For determining patient hypersensitivity by means of the scratch test protein extracts Arlington are supplied in vials containing either 15, 25 or 50 mg of the powdered protein material and in 1 cc and 3 cc vials containing a 1:500 solution of the protein material for intradermal testing.

Alaska Seal¹⁴ Allspice²¹ Almond³ Aniseed³ Apple¹¹ Apricot³ Artichoke¹¹ Asparagus²¹ Banana²¹ Barley²¹ Bass (Black)³ Bass (Sea)³ Bean²¹ Beater¹⁴ Beef²⁰ Beet²¹ Blackberry³ Black-eyed Pea¹¹ Blueberry³ Blue Fish³ Bran (Wheat)²¹ Brazil Nut³ Broccoli²¹ Brussels Sprouts²¹ Buckwheat²¹ Butterfish³ Cabbage²¹ Cabbage (Red)²¹ Calves Brains²⁰ Camel Hair¹⁴ Cantaloupe³ Caracul²¹ Carp³ Carrot¹¹ Casaba³ Cassia¹¹ Cashew Nut³ Castor Bean³ Catfish³ Cat Hair¹⁴ Cattle Hair¹⁴ Cauliflower²¹ Celery²¹ Celery Cabbage¹¹ Celery, German (Celeriac)¹¹ Cheese (Emmentaler)³ Cheese (Edam)³ Cheese (Gruyere)³ Cheese (Muenster)³ Cheese (Swiss)³ Cherry³ Chestnut³ Clam (Hard)³ Clam (Soft)³ Corn²¹ Cotton¹¹ Crabapple³ Cucumber³ Cury¹⁴ Duck²⁰ Duck (Wild)³ Egg (Hens)³ Egg (Turkey)³ Fig³ Filbert³ Ginger³ Glue³ Grape³ Grapefruit³ Hairy³ Hog Hair¹⁴ Horse Radish²¹ Horse Kidney (Beef)¹¹ Lettuce²¹ Lima Bean²¹ Lycopodium²¹ Mouse Hair¹⁴ Mustard³ Nutmeg³ Oyster³ Oyster (Raw)³ Peanut³ Pear³ Perch³ Pickle³ Pompano³ Poppy Seed³ Quince Seed³ Red Cedar²¹ Red Sardinia³ Scallop²⁰ Silk¹⁴ Skunk¹⁴ Squirrel¹⁴ Strawberry³ Potato²¹ Swiss Tobacco³ Tomato³ Turkey²⁰ English)³ Walnut (Whole)³ Wheat (Whole)¹⁴ Wheat (Leavening)²¹ Wheat

extractions with twentieth normal sodium hydroxide solution 1 lb

filters. The finished products are tested for sterility according to the methods required by the U S Public Health Service. The protein content of the sterile solution is estimated by multiplying the nitrogen content determined according to the Kjeldahl method, by the factor 6.25, dilutions are made on the basis of the estimated protein content.

The dried protein material used in the preparation of the extracts marked 1 is prepared as follows. The hard shells are removed, nuts are ground and extracted with carbon tetrachloride or acetone to remove oils. The residue is extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 2 is prepared as follows. The edible portion is separated from the nonedible parts (scales, bones and so on) and finely ground. The material is then extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 3 is prepared as follows. The material is washed in acetone and ether and then ground and sifted.

The dried protein material used in the preparation of the extracts marked 4 is prepared as follows. The seeds are separated and the material chopped fine. An extract is made sufficient tenth normal sodium hydroxide solution being used to make the mixture alkaline to litmus. The extract is filtered and neutralized and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 5 is prepared as follows. The material is chopped and after mixing with thymol is spread on trays to dry. The dried material is ground fine and extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extract marked 6 is prepared as follows. Whites of eggs are mixed thoroughly with two volumes of distilled water, heated to 80 C and made faintly acid. The precipitate is filtered off and discarded. To the filtrate are added two and one half volumes of acetone. The precipitate formed is collected, dried and sifted.

The dried protein material used in the preparation of the extract marked 7 is prepared as follows. Egg yolks are thoroughly mixed and washed in acetone and ether to remove fat. The residue is extracted with 10 per cent sodium chloride solution. The extract is filtered off and placed in a dialyzer. The precipitate is collected, washed in distilled water, dried and sifted.

The dried protein material used in the preparation of the extract marked 8 is prepared as follows. Skimmed milk is diluted with two volumes of distilled water. Diluted hydrochloric acid is added until the casein settles out. The casein is filtered off and the filtrate neutralized and concentrated in vacuo. Ammonium sulfate is added to saturation point and the precipitate redissolved in distilled water.

The solution is placed in a dialyzer and allowed to remain until the sulfate test is negative. The lactalbumin, precipitated by the addition of two and one half volumes of acetone is collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 9 is prepared as follows. The material is dissolved in or diluted with distilled water. The solution is filtered if necessary and the protein precipitated with acetone. The precipitate is washed with acetone, dried, ground and sifted.

The dried protein material used in the preparation of the extract marked 10 is prepared as follows. The five protein fractions present in and separately prepared from wheat flour are mixed.

The dried protein material used in the preparation of the extract marked 11 is prepared as follows. Wheat flour is extracted with distilled water. The extract is collected, filtered clear and made slightly acid. It is then heated to 65 C and the precipitate filtered off, dried and sifted.

The dried protein material used in the preparation of the extract marked 12 is prepared as follows. The filtrate obtained after removing

extract is concentrated in vacuo, dried, ground and sifted

The dried protein material used in the preparation of the extract marked 15 is prepared as follows. Wheat flour is extracted with distilled water, 10 per cent sodium chloride solution and 80 per cent alcohol. The residue remaining is then extracted with tenth normal sodium hydroxide solution. The extract is neutralized with diluted

The dried protein material used in the preparation of the extract marked 17 is prepared as follows. The material is dissolved in five volumes of distilled water and then centrifuged. The supernatant liquid is discarded, the residue is dried and powdered.

The dried protein material used in the preparation of the extracts marked 18 is prepared as follows. Equal parts of the egg white and egg yolk proteins are mixed.

The dried protein material used in the preparation of the extract marked 19 is prepared as follows. The material is dissolved in five volumes of distilled water and then centrifuged. The supernatant liquid is discarded, the residue is dried and powdered. The casein solution is washed.

The dried protein material used in the preparation of the extracts marked 20 is prepared as follows. After removal of feathers bones

tein extract Arico is prepared by separating the whites of fresh eggs from the yolks. The egg whites are added to an equal volume of physiologic solution of sodium chloride passed several times through

2. Wheat (whole) protein extract Arico. Part I. Wheat flour is extracted with 10 per cent sodium chloride solution, chloroform being used as a preservative. The extract is filtered off and dialyzed against running water until freed from salt, toluene and chloroform being used

as preservatives. The solution is then centrifuged and the supernatant fraction reduced in volume in vacuo. The precipitate from dialysis is

combined. Dilutions are then made as in the general method.

ENDO PRODUCTS, INC.

Allergenic Extracts: The following extract is marketed in treatment set packages of four 10 cc vials containing, respectively, slightly more than 1 cc of a 25 per cent, 0.25 per cent, 0.025 per cent and 0.0025 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin) and four 10 cc vials containing 9 cc of diluting fluid (0.4 per cent phenol in isotonic solution of sodium chloride), in maintenance treatment packages of one 10 cc vial containing 1 cc of a 25 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin) and one 10 cc vial of diluting fluid (0.4 per cent phenol in isotonic solution of sodium chloride), in bulk treatment packages of 5 and 10 cc containing a 25 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin). The extract is also supplied in special treatment packages of one 10 cc vial containing 4 cc of a 25 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin) and one 10 cc vial containing 6 cc. of diluting fluid (0.4 per cent phenol in isotonic solution of sodium chloride).

House Dust (Purified Concentrate)

Allergenic extract house dust (purified concentrate) Endo is prepared from dust obtained from mattresses and household furniture.

A mixture of 1 part by weight of house dust and 2 parts by volume of distilled water is covered with toluene and extracted while stirring at 0 to 5 C. for seventy-two hours. The aqueous extract is separated

solution w/v (adjusted by low temperature vacuum distillation if necessary), obtained by dialysis, sodium chloride is added (18 Gm per hundred cc)
 filter The
 sterilized
 constitutes
 prepared
 filling into sterile vials by aseptic technique

Allergenic Extracts Diagnostic: The following extract is marketed in packages of a single vial, with accompanying applicator containing 1 cc of a 1:200 solution (0.5 per cent) of the original extract in 50 per cent glycerin

House Dust (Purified) Concentrate

This extract, for use by the scratch method and cutaneous testing is prepared in much the same manner as the allergenic extract Endo, for treatment just described. The procedure is the same up to the point of dialysis whereupon the extract for diagnosis undergoes the following treatment. To the solution obtained immediately before dialysis ammonium sulfate is added (60 Gm per hundred cubic centimeters). The coagulated material is centrifuged. The separated solid is dissolved in one-half the original volume of distilled water and the ammonium sulfate precipitation is repeated. The solid separated by centrifugation is suspended in a small volume of water and dialyzed until the solution in the sac does not respond to tests for the sulfate ion. The dialyzed solution is centrifuged to remove a small amount of suspended solids and the solution is adjusted (by vacuum distillation at low temperature if necessary) to contain 1 per cent of dissolved solids. Sufficient sodium chloride is added to yield a 1.8 per cent solution with respect to sodium chloride. The solution is diluted with an equal volume of glycerin and filtered through a Seitz filter. This 0.5 per cent solution constitutes the allergenic extract purified house dust concentrate for diagnosis by scratch testing.

HOLLISTER STIER LABORATORIES

Protein Extracts Diagnostic: Food, animal epidermal and other protein extracts are supplied for diagnostic purposes in 1 cc ampuls fitted with capillary tube and rubber bulb and containing sufficient material for approximately 25 tests.

LEDGER LABORATORIES, INC.

Allergenic Extracts: 6 cc. vials

Extracts marketed in undiluted form

Apple², Apricot², Artichoke², Blackberry², Blueberry², Cantaloupe², Cherry², Cranberry², Currant (Red)², Date², Fig², Gooseberry², Grape², Grapefruit², Hackberry², Juniper Berry², Lemon², Lime Juice², Melon (Cantaloupe)², Melon (Honey Dew)², Peach², Pear², Pineapple², Plum², Pomegranate², Prune², Quince², Raisin², Raspberry (Red)², Rhubarb², Strawberry², Tangerine², Watermelon²

Extracts marketed in undiluted form and in 1:10 dilution

Alfalfa², Alligator Pear², Allspice², Anchovy², Arrowroot², Artichoke (Jerusalem)², Asparagus², Banana², Barley², Bass², Bay Leaf², Bean (Kidney)², Bean (Lima)², Bean (Mexican)², Bean (Navy)², Bean (Pea)², Bean (String)², Beef², Beet², Bluefish², Broccoli², Brussels Sprouts², Butterfish², Cabbage², Carp (Fresh)², Carrot², Casein², Catfish², Cauliflower², Caviar², Celery², Chicken Meat², Chicory², Chive², Cinnamon², Citron², Clam², Clove², Codfish², Coffee Bean²

Corn (Sweet)¹ Carnmeal² Crab Meat² Cucumber² Dandelion² Deer Meat² Dill Leaves² Duck Meat² Eel² Egg Plant² Endive² Flounder² Fluke² Frog's Legs² Garlic² Ginger² Goat Meat² Goat Milk² Goose Meat² Green Pea² Guinea Hen Meat² Haddock² Halibut² Hemp² Henna² Herring² Hops² Horse Meat² Horseradish² House Dust (Mattress)² Kale² Lamb² Leek² Lentil² Lettuce² Lobster² Mace² Mackerel² Milk (Cow's)² Mushroom² Nutmeg² Oat (Meal)² Okra² Olive² Onion² Orange² Oyster²

fish² Whiting (Eul)²

Extract marketed in undiluted 1 10 and 1 100 dilution
Horse Serum²

Extract marketed in undiluted form and 1 100 dilution
Pyrethrin²

Extract marketed in 1 10 dilution
Jack Bean²

Extract marketed in dilutions representing 1 mg and 0.001 mg of nitrogen per cc
Silk (Silkworm)²

Extract marketed in dilutions representing 0.5 mg and 0.05 mg of nitrogen per cc
Chocolate²

Extract marketed in dilutions representing 0.2 mg and 0.1 mg of nitrogen per cc
Sheep Dander (Wool)²

Extract marketed in dilutions representing 0.2 mg and 0.01 mg of nitrogen per cc
Cow Dander (Hair)²

Extract marketed in dilutions representing 0.2 mg 0.01 mg and 0.001 mg of nitrogen per cc
Flaxseed²

Extracts marketed in dilutions representing 0.2 mg and 0.001 mg of nitrogen per cc
Anise Seed² Canary Seed² Cottonseed²

Extracts marketed in dilutions representing 0.1 mg of nitrogen per cc

Canary Feathers (Dander)² Feathers (Chicken Duck Goose) (Dander)² Goat Dander (Hair)² Parrot Feathers (Dander)² Pigeon Feathers (Dander)² Turkey Feathers (Dander)²

cation. The coagulum formed is separated at once from the extract by filtration. The toxin free extract is sterilized by filtration and standardized on the basis of its nitrogen content.

The product marked 13 is prepared by the following method. The dried worms are ground and treated with toluene and ether until practically fat free. The residue is extracted with the buffered solution. The dialyzed extract is sterilized by Berkefeld filtration and standardized according to its nitrogen content.

The product marked 14 is prepared by the following method. Fresh fat free milk is treated with rennin. The coagulum formed is defatted by separate extractions with acetone, toluene and ether. The resulting material is dried under vacuum and powdered. The defatted powder is extracted by constant stirring, with the buffered saline solution. The extract is sterilized by filtration and standardized on the basis of nitrogen content.

Glycerinated Allergenic Protein Extracts These extracts for use exclusively by the scratch method of cutaneous testing, are prepared in the same manner as the allergenic extracts Lederle described above. However they contain glycerin and are much more concentrated. They are supplied in capillary tubes providing sufficient material for one scratch test.

PARKE, DAVIS & COMPANY

Protein Extracts Diagnostic Protein extracts derived from food, plant, bacterial and other proteins in the form of paste, the base of which is a mixture of glycerin and glycerite of starch. One part of paste represents one part of original material. The extracts afford a convenient means of carrying out the diagnostic scratch test. They are supplied in collapsible tubes containing 1.5 Gm. of material, enough for approximately 50 tests.

Group Protein Extracts Diagnostic A mixture of equal parts of two or more protein extracts diagnostic-P. D. & Co., supplied in collapsible tubes containing 1.5 Gm. of the mixture. The protein constituents of each group are selected on the basis of their class relationships.

WYETH, INCORPORATED

Protein Extracts Diagnostic These extracts for the diagnosis of protein sensitivity by the intracutaneous method are supplied in 1 cc. size cartridge ("Tubex") vials containing sufficient protein material of appropriate dilution for twenty to thirty tests. The test sets are accompanied by a suitable cartridge syringe, sterile needles and three cartridge vials each of epinephrine hydrochloride solution, buffered saline solution and distilled water. After injection of each extract the needle should be flushed with distilled water to avoid contamination with the extract used previously.

Extracts marketed in dilution representing 0.05 mg. of nitrogen per cubic centimeter.

Apple¹ Apricot² Artichoke³ Asparagus⁴ Banana⁵ Beef⁶ Beets⁷ Blackberry⁸ Broccoli⁹ Cabbage¹⁰ Cantaloupe¹¹ Carrot¹² Cauliflower¹³ Celery¹⁴ Cherry¹⁵ Chicken¹⁶ Cucumber¹⁷ Dates¹⁸ Endive¹⁹ Fig²⁰ Garlic²¹ Grape²² Grapefruit²³ Green Pea²⁴ Leeks²⁵ Lemon²⁶ Lentil²⁷ Lettuce²⁸ Mushroom²⁹

Mutton,³ Olive,³ Onion,⁴ Orange,³ Parsley,³ Peach,³ Pear,³ Pepper (Green),³ Pineapple,⁴ Plum,³ Pork,³ Potato (Sweet),³ Potato (White),³ Prune,³ Pumpkin,³ Radish,³ Raspberry,³ Rhubarb,³ Spinach,⁴ Squash,³ Strawberry,⁴ Tomato,³ Turnip,³ Watercress,⁴ Watermelon,³

Extracts marketed in dilutions representing 001 mg of nitrogen per cubic centimeter

Alfalfa (Hay),⁴ Bay Leaves,³ Bran,⁴ Chicken Feathers,³ Cinnamon,⁴ Clove,⁴ Coffee,⁴ Corn (Sweet),³ Duck Feathers,³ Ginger,⁴ Goat Hair,⁴ Goose Feathers,³ Hops,³ Kidney Bean,⁴ Lactalbumin,³ Milk (Cheeses),³ Nutmeg,⁴ Oats,⁴ Rice,⁴ Rice Powder,⁴ Rye,⁴ Tea,⁴ Thyme,⁴ Wheat,⁴ Wool,⁴

Extracts marketed in dilutions representing 0005 mg of nitrogen per cubic centimeter

Brasil Nut,⁴ Cashew Nut,⁴ Chestnut,⁴ Cocoa (Chocolate),³ Hazel Nut,⁴ Hickory Nut,⁴ Lima Bean,⁴ Navy Bean,⁴ Pea,⁴ Pecan,⁴ Pistachio,⁴ Soy Bean,⁴ String Bean,⁴

Extracts marketed in dilutions representing 0001 mg of nitrogen per cubic centimeter

Alder,⁴ Almond,⁴ Anise Seed,⁴ Ash (Oregon),⁴ Ash (White),⁴ Barley,⁴ Bass,⁴ Beaver,³ Beech,⁴ Bermuda Grass,⁴ Birch,⁴ Bluefish,⁴ Camel Hair,⁴ Chickadee,⁴ Coconut,⁴ Elm,⁴ Ermine,⁴ False Haddock,⁴ Halibut Grass,⁴ June Grass,⁴ Leopard,⁴ Lobster,⁴ Orchard Grass,⁴ Poplar,⁴ Pyreth Red Top,⁴ Russian al,⁴ Shad,⁴ Shrimp,⁴ Grass,⁴ Sycamore (English),⁴ Wrasse,⁴

Extracts marketed in dilutions representing 00005 mg of nitrogen per cubic centimeter

Egg (Chicken),³ Mustard,⁴ Glue (Fish),¹⁰

Extract marketed in dilutions of 1/10

House Dust,⁴

Extract marketed in dilutions of 1/100

Horse Serum,⁴

Protein extracts diagnostic Reischel are prepared from the various substances by extraction with a slightly alkaline buffered saline solution composed of sodium chloride 0.5 per cent sodium bicarbonate 0.275 per cent and phenol 0.4 per cent in distilled water. Carbon dioxide is then bubbled into the extracts until they become colorless when tested to phenolphthalein. The products are standardized on the basis of the nitrogen content per unit volume (Kjeldahl method). Certain products, namely house dust and horse serum, not lending themselves to such standardization are therefore marketed in dilutions of 1/10 and 1/100 respectively.

Extracts marked 1 are prepared by the following method. The juices are squeezed and separated from pulp by filtration. The pH is adjusted to 7.4 with sodium carbonate diluted with buffered alkaline saline solution, filtered, standardized and diluted to appropriate strength.

Extracts marked 2 are prepared by the following method. The crude material is ground as fine as possible. Alkaline buffered solution is added to the pulp and allowed to extract under toluene for from one to

two days at room temperature. After the toluene has been removed in a separator the extract is filtered, standardized and diluted to appropriate strength.

Extracts marked 3 are prepared by the following method. After the removal of all fat and tendons, the muscle fibers are then ground as fine as possible. The ground material is washed with warm (50 C.) toluene until entirely free of fats. The toluene washings are discarded and the residue is washed with alkaline buffered saline solution for one to two days. The extract is filtered,

Extracts marked 4 are prepared by the following method. The materials are ground as fine as possible, the powder or flour is washed with ether and toluene until the washings are clear and colorless. The washings are discarded and the residue is dried. The dried residue is extracted with alkaline buffered saline solution under toluene at room temperature for from one to two days. The extract is filtered through a Buchner funnel and the toluene removed in a separator. The extract is filtered, standardized and diluted to appropriate strength.

Extracts marked 5 are prepared by the following method. The materials are washed with ether and toluene, dried and extracted under toluene for from one to two days at room temperature. The extract is cleared of toluene in a separator, filtered, standardized and diluted to appropriate strength.

Lactalbumin, marked 6 is prepared by the following method. The casein is precipitated with renin and the lactalbumin after neutralization with sodium bicarbonate, is precipitated from the resulting whey with acetone. The lactalbumin is then extracted with alkaline buffered saline solution, filtered, standardized and diluted to appropriate strength.

Egg (Chicken), marked 7, is prepared by the following method. The egg is separated from the shell and the yolk is washed with water and alcohol.

The egg is then extracted with alkaline buffered saline solution for one to two days. The extract is filtered, standardized and diluted to appropriate strength.

Horse Serum, marked 9, is prepared by the following method. Normal Horse Serum is treated with phenol, so that the final concentration of phenol is 0.4 per cent. It is then diluted to proper strength with alkaline buffered saline solution.

Glue (Fish), marked 10, is prepared by the following method. The glue is diluted in alkaline buffered saline solution, standardized and diluted to appropriate strength with alkaline buffered saline solution.

Fungus Extracts

ABBOTT LABORATORIES

Fungus Extracts: 2 cc, 5 cc and 30 cc vials

Alternaria spp, *Aspergillus fumigatus*, *Aspergillus niger* Group, *Cephalothecium roseum*, *Hormodendrum spp*, *Monilia sitophila*, *Mucor spp*, *Penicillium rubrum*, *Ustilago zeae* (Corn Smut), Yeast

The yeast extract is prepared from dried brewers yeast, the *Alternaria spp* extract is prepared from the dried mass of spores with its supporting mycelium, the other extracts are prepared from the dried spores alone. The material is extracted at room temperature with a menstruum consisting of equal volumes of glycerin and a solution containing sodium chloride 5 Gm and sodium bicarbonate 2.7 Gm in distilled water 1000 cc for from four to five days and is clarified and sterilized by Berkefeld filtration. The finished liquid is a 5% W/V extract of the dried fungus material each cubic centimeter representing 0.05 Gm. of dried material.

Pollen Extracts

ABBOTT LABORATORIES

Concentrated Pollen Extracts: 2 cc and 5 cc vials

U S patent 1,977,803 (Oct 23 1934, expires 1951)

Annual Sage, Arizona Ash, Ash, Bermuda Grass, Black Walnut, Biennial Sage, Blue Grass, Box Elder, Burweed, Marsh Elder, Canada Blue Grass, Cocklebur, Corn, Casmoe, Coastal Sagebrush, Cottonwood, Crab Grass, Dandelion, English Plantain, Lim. False Ragweed, Giant Ragweed, Goldenrod, Goose Grass, Hemp, Hickory, Johnson Grass, Lamb's Quarters, Marsh Elder, Mixed Grass (Blue Grass Timothy, Orchard Grass, Red Top and Sweet Vernal Grass in equal parts), Mixed Ragweed (Ambrosia elatior and Ambrosia trifida), Mountain Cedar, Mugwort, Oak Concentrated, Orchard Grass, Ox Eye Daisy, Palmer's Amaranth, Plantain, Prairie Sage, Quailbrush, Redroot Pigweed, Red Sorrel, Redtop, Russian Thistle, Sagebrush, Short Ragweed, Slender False Ragweed, Southern Ragweed, Spiny Amaranth, Sudan Grass, Sunflower, Sweet Vernal Grass, Sycamore, Timothy, Western Ragweed, Western Water Hemp, Yellow Dock, Yellow Fox Tail

Concentrated pollen extracts Abbott are prepared by extracting dried pollen with a menstruum composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water. The extract is clarified and sterilized by filtration. The finished liquid is a 3 per cent extract of the dried pollen each cubic centimeter representing 0.03 Gm. of dried pollen (30,000 units).

Pollen Extracts. Extracts marketed in the following forms: Treatment sets of 16 vials containing for each consecutive dose (1 to 16, inclusive) 10, 20, 40, 70, 100, 200, 400, 700, 1,000, 1,500, 2,000, 3,000, 4,000, 5,000 and 5,000 pollen units, respectively accompanied by a vial containing three 0.025 Gm capsules ephedrine hydrochloride.

U S patent 1,977,803 (Oct. 23 1934, expires 1951)

Mixed Grass (Timothy, June Grass, Orchard Grass, Red Top and Sweet Vernal Grass in equal proportions), Ragweed (Ambrosia elatior and Ambrosia trifida)

Extracts marketed in special dilution sets

Mixed Ragweed Pollen Extract Decimal Dilution Set. A mixture of equal parts of short and giant ragweed pollen extract marketed in packages of four vials containing respectively, 5 cc. of a 1:10,000 dilution (100 pollen units per cubic centimeter), 5 cc. of a 1:1,000 dilution (1,000 pollen units per cubic centimeter) and two 5 cc vials of a 1:100 dilution (10,000 pollen units per cubic centimeter).

Mixed Grass Pollen Extract Decimal Dilution Set. A mixture of equal parts of June grass, timothy, orchard grass, redtop and sweet vernal grass pollen extracts marketed in packages of four vials containing respectively 5 cc. of a 1:10,000 dilution (100 pollen units per cubic centimeter), 5 cc. of a 1:1,000 dilution (1,000 pollen units per cubic centimeter) and two 5 cc vials of a 1:100 dilution (10,000 pollen units per cubic centimeter).

Pollen extracts Abbott are prepared by extracting dried pollen with a menstruum composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water. The extract is clarified and sterilized by filtration. The finished liquid is a 3 per cent extract of the dried pollen each cubic centimeter representing 0.03 Gm. of dried pollen (30,000 units). Dilutions are prepared with additional menstruum.

Pollen Extracts Diagnostic For skin testing the extracts are supplied in vials of 3 and 50 mg capillary tubes each tube providing sufficient material for one scratch test

THE ARLINGTON CHEMICAL COMPANY

Pollen Extracts The following extracts are marketed in sets of five vials representing graduated concentrations namely 1 in 10 000 1 in 5 000 1 in 1 000 1 in 500 and 1 in 100 respectively

For diagnostic purposes concentrated solutions of the pollen extracts are supplied in capillary tubes containing sufficient material for one test and in 1 cc vials containing enough material for approximately 15 tests Dry pollens suitable for use in carrying out diagnostic scratch tests are supplied in vials containing 50 mg

Ash Bern da Grass Birch Mixture (White Birch Black Birch and Yellow Birch in equal parts) Birch Box Elder Burning Bush Burr Ragweed Burweed California Mugwort Carleweed Cocklebur Corn Cottonwood Elm Golden Rod Goosefoot Grass Mixture No 1 (Timothy June Grass Orchard Grass and Red Top in equal parts)

Oak in equal parts) Oak Olive Orchard Grass Pigeon Plantain Poplar Prairie Ragweed Prairie Sage Prickly Ragweed Dwarf and Giant Mixture (equal parts of each) Ragweed Mixture Plus Burweed March Elder Ragweed (Ambrosia trifida) Ragweed (Ambrosia artemisiifolia) Redtop Russian Thistle Rye Grass Sagebrush Shad Scale Slender Ragweed Spiny Amaranth Sunflower Sweet Lernal Grass Sycamore Timothy Velvet Grass Walnut Western Ragweed (Giant) Western Water Hemp Willow

Pollen extracts Arlington are prepared by the method of Walker (*Am J M Sc* 137:409 [March] 1919). To 0.5 Gm of the dry pollen is added 44 cc of sterile physiologic solution of sodium chloride and the mixture is shaken thoroughly at frequent intervals for twenty four hours. Sufficient absolute alcohol (7 cc) is then added to make the alcohol content 14 per cent. The mixture is thoroughly shaken at frequent intervals for twenty four hours after which it is centrifugalized at high speed and the supernatant fluid is drawn off with a pipette. This liquid represents 1 part of pollen in 100 parts of a solvent which consists of about 14 per cent alcohol added to isotonic solution of sodium chloride. This 1 in 100 solution is used as stock and from it other dilutions such as 1 in 500 1 in 1 000 1 in 5 000 and 1 in 10 000 are made. Cresol is added as a preservative.

BARRY ALLERGY LABORATORY, INC

Allergenic Extracts The following extracts are marketed in complete treatment set packages consisting of four vials representing graduated concentrations namely 1 in 33 1/3 1 in 500 1 in 10 000 and 1 in 100 000 respectively and in single

vial packages containing 5 cc. of a 1:33½ solution; 0.5 per cent phenol (phosphate buffer, pH 7.4) used as preservative.

Grass Mixture (Spring), (June Grass, Timothy, Red Top, Sweet Vernal Grass and Orchard Grass, in equal proportions), Ragweed (Large and Small Ragweed, in equal proportions)

liquid contains 8 per cent of glycerin and 0.4 per cent of cresol
The pollen unit corresponds to 0.001 mg of dried pollen

CUTTER LABORATORIES

Pollen Extracts: The following extracts are marketed in complete treatment set packages consisting of three vials representing graduated concentrations, namely, 1 in 10,000, 1 in 500 and 1 in 33½, respectively; and in single vial packages containing 5 cc of a 1:33½ solution, 0.5 per cent phenol (phosphate buffer, pH 7.4) used as preservative

Acacia, Alder, Alfalfa, Alkali Rye Grass, Alkali Weed, All Scale, Almond, Annual Blue Grass, Annual Salt Bush, Ash, Aspen, Bent Grass, Bermuda Grass, Birch, Black Walnut, Box Elder, Bract Scale, Brome Grass, Broncho Grass, Burning Bush, Canada Blue Grass, Canary Grass, Careless Weed, Chapparal Broom, Chest Grass, Chrysanthemum, Clover, Coast Sagebrush, Cocklebur, Common Ragweed, Coreopsis, Corn, Cosmos, Cottonwood, Cultivated Rye, Curly Dock, Dahlia, Dandelion, Date, Deodor Cedar, Elm, English Walnut, Euca-

Oak, Wild Oak, Willow, Yellow Pine

Pollen extracts Cutter are prepared by extracting the dried pollen with a menstruum composed of 50 per cent of glycerin in a buffered physiologic salt solution to which 0.5 per cent phenol has been added. The buffer is prepared by mixing 100 cc. of M/3 KH_2PO_4 (45.4 Gm KH_2PO_4 per liter) and 900 cc of M/3 solution $Na_2HPO_4 \cdot 12H_2O$ (119.0 Gm $Na_2HPO_4 \cdot 12H_2O$ per liter). Two per cent of this buffer solution is used to yield a final pH (after sterilization) of 7.4.

The pollen extract is clarified by Berkefeld filtration. The finished liquid is a 3 per cent extract of the dried pollen, each 1 cc representing 0.03 Gm of dried pollen. Dilutions containing the equivalent of 0.002 Gm of pollen per cc. and dilutions containing the equivalent of 0.0001 Gm of pollen per cc are prepared by diluting the 3 per cent extract with the same solution as was used for extraction.

HOLLISTEN-STIER LABORATORIES

Pollen Extracts. The following extracts are marketed in treatment sets of four vials containing, respectively 10, 100,

1 000 and 10 000 pollen units per cubic centimeter preserved with 50 per cent glycerine accompanied by one vial of sterile distilled water for diluting the extract, and in single vials of 1 2 5 10 and 20 cc quantities

For diagnostic purposes these pollen extracts are marketed in ampuls containing 0.5 cc. The ampuls are fitted with a capillary tube and rubber bulb and provide sufficient extract for eight to ten tests

Acacia Alder Alfalfa Ash (White) Aspen Atriplex Awnless Brone Grass Beech Bermuda Grass Blue Birch, Grass Box Elder Canada Blue Grass Careless Weed Cedar (Mountain) Cheat Clover Cocklebur Corn Cottonwood (Common) Crested Koeleria Da delos Dock (Yellow) Eastern Ragweed Elm English Plantain Fescue (Meadow) Giant Poverty Weed Goldenrod Johnson Grass Kentucky Blue Grass Kochia Lambs Quarters Maple (Hard) Mugwort Oak (White) Olive Orchard Grass Perennial Rye Grass Pine (Yellow) Quack Grass Redroot Pigweed Redtop Riss on Thistle Sage (Common) Sage (Pasture) Sage (Prairie) Sagebrush (Common) Sanbergs June Grass Sheep Sorrel Short Ragweed Spear Scale Spring Birch Sugar Beet Sweet Fernal Grass Sycamore Timothy Velvet Grass Walnut (English) Western Ragweed Western Water Hemp Wheat (Cultivated) Willow and Wormwood

Pollen extracts Hollister Stier are prepared by extracting the dried pollen with a menstruum composed of 50 per cent of glycerin 5 per cent of sodium chloride and 45 per cent distilled water. The extract is clarified by Setz filtration. The finished liquid is a 5 per cent extract of the dried pollen each cubic centimeter representing 50 000 pollen units 1 unit corresponding to 0.001 mg of dried pollen

LEDERLE LABORATORIES INC

Pollen Antigens The following pollen antigens are marketed in packages of three 3 cc vials containing 100 1 500 and 20 000 pollen units per cubic centimeter, respectively, and also in individual vials of each unitage

For diagnosis by the scratch test method the extracts are supplied in individual capillary tubes containing enough material for one test

Acacia Annual Salt Bush Ash Beech Bermuda Grass Birch Black Walnut Careless Weed, Cocklebur Cottonwood Giant Ragweed Green Sage Hickory Johnson Grass June Grass (Poa pratensis) Lambs Quarters Marsh Elder Mesquite Mixed Grasses (June Grass parts) e Sage igweed Redtop er Rag Sweet Western

Ragweed Yellow Dock

The following mixtures of pollen antigens are marketed in package forms designated Series D five vials each containing 3 000 pollen units and five vials of sterile diluent with which to make the proper dilution of each dose also in packages designated Complete Series Packages containing 15 graduated doses

(25, 5, 10, 20, 35, 60, 100, 165, 275, 450, 750, 1,200, 1,800, 2,400 and 3,000 pollen units respectively), and in packages containing three 3 cc vials 20,000 units per cc and in packages containing six 3 cc vials, 20,000 units per cc.

Mixed Grasses (June Grass Orchard Grass Sweet Vernal Grass Red Top and Timothy in equal parts) Ragweed Combined (Common and Giant Ragweed in equal parts)

Pollen antigens-Lederle are prepared by extracting dried pollen in a quantity of extracting fluid calculated to give 30,000 pollen units per cubic centimeter according to a nitrogen-determination previously done on a sample of each stock of dried pollen (the pollen unit having been arbitrarily chosen as the equivalent of 0.00001 mg. of total nitrogen). Extraction is carried out as follows: Pollen is thoroughly mixed with an aqueous solution containing 50 per cent glycerin, 0.5 per cent sodium chloride, 0.27 per cent sodium bicarbonate and 0.45 per cent phenol for two hours at room temperature and after another thorough mixing stored overnight in the ice-box (3-5°C.). After the extracting period the mixture is again thoroughly shaken and is immediately filtered.

NATIONAL DRUG COMPANY

Allergenic Extracts. The following pollen extract is marketed in packages of three 5 cc vials representing, respectively, 2,500, 5,000, 10,000 and 25,000 nitrogen units per cubic centimeter, and in single 5 cc syringe packages of 10,000 and 25,000 nitrogen units per cc. for maintenance dosage. Each package is accompanied by a 1 cc vial 150 units per cc concentration for preliminary dosage or determination of degree of sensitivity.

For determining patient hypersensitivity by means of the scratch test the extracts are supplied in individual capillary tubes containing sufficient material for one test.

The following preparations are marketed in 5 and 15 cc ampul vial packages representing, respectively, 2,500, 5,000, 10,000 and 25,000 nitrogen units per cubic centimeter.

Ragweed (Giant and Dwarf Ragweed in equal parts), Mixed Grass (Timothy 75 per cent June Grass Orchard Grass Red Top Rye, and Sweet Vernal Grass each 5 per cent)

Allergenic extracts are prepared by the following method: The pollen is weighed and extracted with ether. After removal of the ether the material is mixed with the extracting liquid consisting of a 0.5 per cent sodium chloride solution containing approximately 0.28 per cent of sodium bicarbonate and 0.4 per cent of phenol and then covered with toluene. After four days during which time the mixture is shaken once or twice daily the supernatant fluid is decanted and the sediment mixed with a second portion of extracting fluid. As soon as the sediment has settled the supernatant fluid is decanted and mixed with the first portion. The combined decanted fluid is then subjected to Berkefeld filtration and tested for sterility. The nitrogen content of the extract is determined and dilutions are prepared on a basis of 0.00001 mg. of nitrogen per unit.

U S STANDARD PRODUCTS COMPANY

Allergenic Extracts. The following pollen extracts are supplied in 5 cc vials containing 20,000 units per cubic centimeter. In addition two of the products (Grasses Combined and Ragweed Combined) are marketed in single treatment set packages of three vials containing respectively 100, 1,000 and 10,000 units

per cubic centimeter and accompanied by a vial containing 2 cc of epinephrine hydrochloride solution 1:1,000. Five tenths per cent of phenol is used as preservative.

For the diagnostic scratch test highly concentrated pollen extract solutions are supplied in individual capillary tubes containing sufficient material for one test.

	Al ³⁺	As ³⁺	Br ⁻	Ca ²⁺	Co ²⁺	Cu ²⁺	Fe ²⁺	H ⁺	Mg ²⁺	Mn ²⁺	Ni ²⁺	Pb ²⁺	Se ²⁻	Si ⁴⁺	Sn ²⁺	Sr ²⁺	Ti ⁴⁺	V ³⁺	Zn ²⁺
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The following product is supplied in 5 cc vials representing 30,000 pollen units per cubic centimeter and in packages of four 5 cc. vials representing, respectively, 100 1000 10 000 and 10 000 pollen units per cubic centimeter

Regusoid Combined (Giant and Common Regusoid in equal parts)

The following product is supplied in 5 cc vials representing 30 000 pollen units per cubic centimeter

Grazes Combined (Bermuda June Grass Orchard Grass Red Top
Street Lernal Grass and Timorhy in equal parts)

Prepared by extracting the dried pollen with a menstruum containing 67 per cent glycerin and 33 per cent of a physiological solution

the 1990s, the number of people in the world who are illiterate has increased from 1.2 billion to 1.5 billion. The number of illiterate people in the world is projected to increase to 1.7 billion by the year 2015. The number of illiterate people in the world is projected to increase to 1.7 billion by the year 2015.

WYTH, INCORPORATED

Allergenic Extract: The following extract is marketed in treatment packages of five 1 cc size cartridge ("Tubex") vials representing graduated concentrations namely 100, 1,000, 10,000, 20,000 and 200,000 pollen units per cubic centimeter. Also in treatment packages of five 1 cc. size cartridge ("Tubex") vials, each representing 20,000 pollen units per cubic centimeter.

Tagweed Combined (Cunt and Short Tagweeds in equal proportions)

The polymer is washed and extracted with ether. After removal of the ether the material is mixed with the extracting liquid consisting of a 0.5 per cent sodium chloride solution containing approximately 0.2 per cent of sodium carbonate and 0.5 per cent of sodium chloride with 4-amine. After three days the emulsion is subjected to alcohol treatment and an equal quantity of strong glycerol is added. The mixture is then tested for the presence of sodium ions on the basis of pyrovanate. It is then emulsified in water to 0.1 mg of latex in 1 ml.

Rhus Extracts

Rhus toxicodendron *Rhus diversiloba* and *Rhus venenata* are commonly known as poison ivy oak and sumach. The first two are so closely related they are often confused. The last is a more distinct species. Poison ivy is prevalent east of the Rocky Mountains while poison oak prevails along the Pacific coast.

Contact dermatitis occurs in susceptible people. It is caused by resinaceous substance extractable from the leaves with alcohol, acetone, and other lipid solvents. The substances extracted from poison ivy and poison oak are closely related chemically and may be used interchangeably for the preseasonal immunization or the treatment of ivy or oak dermatitis. Sensitivity to sumach according to some observers is identical with that of ivy, and ivy extracts have been used for sumach prophylaxis.

According to some observers immunity may be established by the oral administration of highly diluted alcoholic extracts given in gradually increasing doses or by repeated intramuscular injections. The acute dermatitis has been treated by intramuscular injections. These injections are often followed by severe reactions and exacerbations of the dermatitis when caution is not used regarding the dosage. In general when injections of the extract are used for immunization or treatment, frequently given small doses are more satisfactory than a few large doses given at longer intervals.

Ivy preparations are solutions of urushiol for immunization against the dermatitis following contact with poison ivy oak sumach or the lacquer from Japanese Chinese and Indo Chinese lac trees. Acceptable preparations may be made from the fresh new twigs and leaves of any one of the common varieties of poison ivy native to North America. The fresh material should be dried immediately at a low temperature in vacuo then extracted with absolute alcohol ether or acetone. The resulting solutions appear to be stable if kept free of water. Each preparation whether a solution or a dry residue from the evaporated solvent, should be biologically assayed by determining the weakest solution or dilution which will give a satisfactory contact patch test in between 50 to 60 per cent of an adequate sample of the normally exposed adult population. The initial inoculation should be prepared with reference to this assayed solution. Published data indicate that a fraction of a centimeter of a five to tenfold dilution of this solution or an equivalent solution is a safe initial dose in the patient of more than average sensitivity. The subsequent doses should be near but within the tolerance of the patient.

Published data indicate that a series of weekly doses of increasing strength begun long before the ivy season confers some degrees of temporary immunity. Treatment of the acute dermatitis with ivy extracts is contraindicated. Since the excitant is the same in ivy oak sumach and lacquer there need

be no distinction as far as prophylaxis is concerned regarding the source of the extract

POISON IVY EXTRACT.—A solution of a resin extracted from the fresh leaves of *Rhus toxicodendron*

Actions and Uses.—Poison ivy extract is used for prevention or treatment of the symptoms of the dermatitis produced through contact with *Rhus toxicodendron*

Dosage.—In cases of average susceptibility 0.5 to 1.0 cc. may be given intramuscularly, repeated every 2 to 48 hours until relieved. In cases of unusual susceptibility injections of from 0.2 to 0.35 cc. are given, increased or not as indicated. For prophylaxis two injections of 1.0 cc. each may be given two weeks apart.

ABBOTT LABORATORIES

Poison Ivy Extract. Packages of two 1 cc. ampuls. Each cubic centimeter contains 45 mg. of desiccated oily resin in a mixture of sweet almond and peanut oils.

Fresh leaves of *Rhus toxicodendron* are extracted with methyl alcohol, the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll and then treated with 10% sodium phosphate. The precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and isopropyl alcohol in an extraction apparatus. The extractions are evaporated and the residual extract dried at a low temperature.

HOLLISTER STIER LABORATORIES

Poison Ivy Extract. Packages of five ampuls, each containing 0.2 cc. of alcoholic extract, with five ampuls of sterile salt solution for dilution immediately before administration.

Ten Gm. of mature leaves of *Rhus toxicodendron* are dried, pulverized and extracted seventy-two hours in 100 cc. of absolute ethyl alcohol. The extract is decolorized and sterilized by filtration.

MULFORD COLLOID LABORATORIES

Rhus Tox Antigen. Packages of four 1 cc. ampul vials. Each 1 cc. contains 75 mg. of substance dissolved in 35 per cent alcohol.

Freshly gathered leaves of *Rhus toxicodendron* are extracted with ethyl alcohol, the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll and then treated with 10% sodium phosphate. The precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and isopropyl alcohol in an extraction apparatus. The extractions are evaporated and the residual extract dried at a low temperature.

HANKE, DAVIS & COMPANY

Poison Ivy Extract. Packages of six 1 cc. ampuls. A 15 per cent solution of poison ivy extract, *Rhus toxicodendron* (poison ivy)—poison oak) antigen in almond oil.

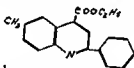
The dried leaves of poison ivy (*Rhus toxicodendron*) are extracted with ethyl alcohol. The resulting extract is dehydrated and decolorized and

the chronic forms seem to yield to cinchophen only in isolated cases. It frequently relieves the pain of sciatica, but not invariably according to Mc Lester (*Arch Int Med* 12 739 [Dec.] 1913). Its use is not recommended except for severe pain which does not yield to safer remedies.

The contraindications are: a condition of the blood, a reaction to the drug, proteinuria, liver disease, circulatory disturbances with resulting metabolic disorders, diets rich in fats and poor in carbohydrates and the onset of any of the symptoms of cinchophen poisoning. The drug should not be employed unless the attending physician feels that the patient's need for it fully justifies the risk, possibly for the relief of pain in certain cases of so called rheumatism, including gout and some types of arthritis when safer substitutes fail to afford relief.

Dosage—In gout the dose of cinchophen is from 0.5 Gm four times a day to 1 Gm three times a day suspended in large quantities of water. In order to prevent the precipitation of free uric acid from the urine with possibly resulting renal colic Weintraub considers it necessary to administer simultaneously 15 Gm of sodium bicarbonate in the course of the first day and from 5 to 10 Gm on the following days. In articular rheumatism Heller prescribed daily doses of from 3 to 5 Gm.

NEOCINCHOPHEN—U S P—The ethyl ester of 6 methyl 2 phenylquinoline 4 carboxylic acid



For description and standards see the U S Pharmacopeia under Neocinchophen and Neocinchophen Tablets.

Actions and Uses—The same as those of cinchophen.

Dosage—0.3 Gm. See dosage statement for Cinchophen.

Para-Aminophenol Derivatives



The members of this group (sometimes known as the phenetidins) are derivatives of para aminophenol ($C_6H_4(NH_2)(OH)$, 14) and are chemically related to aniline (aminobenzene).

CHAPTER II

ANALGESICS AND ANTIPYRETICS

Cinchophen and Derivatives

Cinchophen was introduced in therapeutics under the proprietary name "atophan." It was admitted to the U. S. Pharmacopeia IX as *aacidum phenylcinchoninicum*, the name being later changed to *cinchophenum*. It was omitted from the U. S. P. XI and is now official in the N. F. VII. Cinchophen and its compounds are derived from quinoline carboxylic acid. Cinchophen is 2-phenyl-4-carboxyquinoline. Neocinchophen (introduced as novatophan) is 2-phenyl-4-carbethoxy-6-methylquinoline. Cinchophen has a slightly bitter taste, while neocinchophen is practically tasteless, otherwise their actions are closely similar.

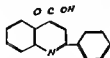
Cinchophen and cinchophen derivatives increase the permeability of the kidneys selectively to uric acid, and therefore greatly increase the excretion of the urates in the urine. Under a purin free diet the amount of uric acid in the blood is reduced one half, when exogenous purins are given the total amount is rapidly excreted so that the content of uric acid in the blood remains at normal or below. The influence of the cinchophen on uric acid excretion is greater and is exerted more promptly than that of sodium salicylate. Its action grows weaker after the first three hours and is practically terminated in nine hours after the administration of the dose. The amount of ammonia and that of total nitrogen in the urine are slightly increased during the action of cinchophen, but not in proportion to the increase in the uric acid of the urine. Cinchophen does not increase the leukocytes, the purin bases or the phosphoric acid. There is no evidence of increased formation of uric acid or of any effect on deposited urates.

While the ordinary doses of cinchophen are usually harmless they are occasionally followed by severe and even fatal effects; these are more frequent with the larger doses. Symptoms of acute intoxication include a sense of oppression in the gastric region with acid eructation and diarrhea, which in some cases can be avoided by the simultaneous use of small doses of sodium bicarbonate. In cystitis it may cause pain in the bladder with hematuria. It occasionally induces a scarlet, an urticaria like or a vesiculous rash. It sometimes induces cardiac distress with dizziness. Excessive doses or the long continued use of moderate amounts may cause damage to the kidney and occasionally gives rise to acute yellow atrophy or to dangerous or fatal hepatitis, usually characterized by the late and relatively abrupt onset of symptoms, the most frequent being jaundice. The appearance of skin rash, vomiting, anorexia, albuminuria, heartburn, diarrhea or jaundice requires the immediate discon-

tinuance of the drug. Relatively small doses occasionally induce symptoms in patients showing idiosyncrasy and it is possible that an attack of hepatitis renders the patient extremely susceptible to further medication at a later date. Especial caution is necessary in the use of cinchophen in the presence of renal insufficiency. The promiscuous use of cinchophen by the public for the relief of pain is obviously dangerous. Fewer cases of poisoning have been reported after neocinchophen but the relative danger of these two has not been determined satisfactorily. There is perhaps some reason to believe that neocinchophen is less likely to prove toxic but the evidence is not conclusive. The same contraindications and precautions should be observed in the use of neocinchophen as in the case of cinchophen.

Avoidance of the contraindications, special attention to the diet and effective supervision of the patient are important but it should not be felt that they render the drug safe. As a supplement to a Council report (J A M A 117 1182 [Oct 4] 1941) on the present status of cinchophen and neocinchophen there was made available a tabulation of the replies to a questionnaire on cinchophen and cinchophen derivatives sent by the Food and Drug Administration. This tabulation revealed that 82 per cent of those questioned feel that these agents are not indispensable in the physician's armamentarium. 71 per cent are of the opinion that cinchophen and cinchophen derivatives do not have any essential therapeutic effect which cannot be accomplished by properly regulated doses of other medicaments. 79 per cent assert that the preparations cannot be administered in therapeutically active doses with confidence that serious deleterious effects will not supervene and 77 per cent are of the opinion that the pathology of cinchophen poisoning cannot be counteracted or cured by specific measures once the symptoms of poisoning have appeared.

CINCHOPHEN—Phenylcinchoninic Acid—Phenylquinolinecarboxylic Acid—N F—2 phenyl 4 carboxyquinoline—Contains when dried to constant weight at 100° C. not less than 99.5 per cent of $C_{16}H_{11}N$, C_6H_5 , $COOH$ 2:4—N F



For description and standards see The National Formulary under Cinchophen and Tablets of Cinchophen.

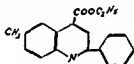
Actions and Uses—Cinchophen is useful in acute gout, it relieves pain in rheumatism and when given in large doses produces diaphoretic effects. It is also useful in acute articular rheumatism.

the chronic forms seem to yield to cinchophen only in isolated cases. It frequently relieves the pain of sciatica but not invariably according to McLester (*Arch Int Med* 12 739 [Dec] 1913). Its use is not recommended except for severe pain which does not yield to safer remedies.

The contraindications to the use of cinchophen seem to include a condition of susceptibility to asthma or hay fever, allergic reaction to foreign proteins, liver disease, circulatory disturbances with resulting metabolic disorders, diets rich in fats and poor in carbohydrates and the onset of any of the symptoms of cinchophen poisoning. The drug should not be employed unless the attending physician feels that the patient's need for it fully justifies the risk, possibly for the relief of pain in certain cases of so called rheumatism including gout and some types of arthritis when safer substitutes fail to afford relief.

Dosage—In gout the dose of cinchophen is from 0.5 Gm four times a day to 1 Gm three times a day suspended in large quantities of water. In order to prevent the precipitation of free uric acid from the urine with possibly resulting renal colic Weintraub considers it necessary to administer simultaneously 15 Gm of sodium bicarbonate in the course of the first day and from 5 to 10 Gm on the following days. In articular rheumatism Heller prescribed daily doses of from 3 to 5 Gm.

NEOCINCHOPHEN—U S P—The ethyl ester of 6-methyl-2-phenylquinoline-4-carboxylic acid.



For description and standards see the U S Pharmacopeia under Neocinchophen and Neocinchophen Tablets.

Actions and Uses—The same as those of cinchophen.

Dosage—0.3 Gm. See dosage statement for Cinchophen.

Para-Aminophenol Derivatives



The members of this group (sometimes known as the phenetidins) are derivatives of para-aminophenol ($C_6H_4(NH_2)(OH)$, 14) and are chemically related to aniline (aminobenzene).

The derivatives have similar pharmacologic properties and as they undergo decomposition in the tissues to yield either para aminophenol or acetylamminophenol any difference in activity may be largely due to the rapidity with which this decomposition occurs.

Acetophenetidin and its congeners are antipyretics and analgesics and have been widely used for these effects. However they are not without danger of untoward effects and should be used with caution. The effects produced may vary not only with the dose but with the individual patient. Undesirable reactions which have been reported following the use of antipyretics include skin eruptions, catarrh, edema of the throat and mouth, nausea and vomiting, disturbances of hearing, confusion, blood changes, heart depression and circulatory collapse. The employment of such drugs in infectious fevers should be most cautious.

Nearly every newly discovered product related to acetophenetidin has been heralded as a safe antipyretic and free from poisonous effects on the blood and heart. Invariably extended clinical experience has shown that all of these preparations have to a greater or less degree an effect on the blood and circulation.

PHENETSAL — Phenetsalum — Salophen — Acetyl *p* aminophenyl Salicylate — Acet *p* aminosolol — 14 Acetamino phenyl Salicylate — $C_6H_5.OH.CO.O.C_6H_4(NHCH_3.CO)$ The salicylic acid ester of 14 acetaminophenol $C_6H_4(NHCH_3.CO)(OH)$

Actions and Uses—The actions of phenetsal resemble those of phenyl salicylate (salol). It is not changed in the stomach but is broken up in the intestine liberating salicylic acid and para aminophenol (which is less toxic than phenol). It acts as an antirheumatic antipyretic and analgesic. It is said to be useful in rheumatism, gout and typhoid fever. Externally it has been applied in psoriasis and itching skin diseases.

Dosage—From 0.3 to 1 Gm. in powder wafers or capsules
Externally in 10 per cent ointment

Tests and Standards—

Phenethyl forms small white crystalline leaflets or powder odorless and tasteless melting at from 14 to 183 C. It is almost insoluble in cold water more soluble in warm water freely soluble in water solutions of the alkalis and in alcohol ether and benzene but not in petroleum benzene.

If its alkaline solution is boiled it gradually becomes blue on continuing the boiling the color is discharged but is again produced on cooling and exposure to air. On the addition of ferric chloride to the

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WINTHROP CHEMICAL COMPANY, INC

Salophen (Powder) bulk Phenetsal—N N R

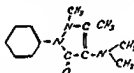
Tablets Salophen 0.325 Gm

U S Trademark 20759

Pyrazolon Derivatives

The preparations in this group are used for their antipyretic and analgesic action and in general are subject to the same caution statements that govern the use of the phenetidin compounds. On taking small doses some susceptible individuals experience nervous and circulatory depression while after large doses instances of collapse have been reported. In the treatment of infectious fevers they as other antipyretics should be cautiously employed. (See the general section Para amino phenol Derivatives) Serious and sometimes fatal granulocytopenia may appear especially in susceptible individuals. The drug should be immediately withdrawn if a skin eruption, dizziness, throat irritation or chill occurs, it should not be administered in large doses or over a long period of time unless repeated leukocyte and differential blood counts are made at frequent intervals. The slightest untoward symptoms are indications for withdrawal of the drug and immediate leukocyte differential count.

AMINOPYRINE—Aminopyrine—U S P—Dimethylaminophenyl dimethylpyrazolon—Pyramidon



For description and standards see the U S Pharmacopeia under Aminopyrine and the National Formulary under Elixir of Aminopyrine and Tablets of Aminopyrine

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menorrhoea or for any other purpose at or near the menstrual period. Special attention is called to the dangerous side actions mentioned in the preceding article Pyrazolon Derivatives

Dosage—From 0.3 to 0.4 Gm most conveniently in the form of tablets a single dose usually sufficing for twenty four hours

ABBOTT LABORATORIES

Tablets Aminopyrine 0.325 Gm

MEYER & Co., INC

Aminopyrine (*Powder*) bulk

THE Wm S MERRELL COMPANY

Tablets Aminopyrine 0.324 Gm

WINTHROP CHEMICAL COMPANY, INC

Pyramidon (*Powder*) bulk

Elixir Pyramidon Each 4 cc contains pyramidon 0.162 Gm in a menstruum containing alcohol 20 per cent

Tablets Pyramidon 0.13 Gm and 0.325 Gm

U S patent exp red U S Trademark

Salicylic Acid Compounds



To avoid the disagreeable taste and gastric symptoms of salicylic acid and its salts esters of salicylic acid have been introduced which are more or less insoluble so that the salicyl radical is liberated only in the intestine or after absorption into the blood. These compounds may exert direct action on the stomach recent work suggests the possibility of gastric ulcer formation if the compounds are not properly diluted or made otherwise tolerable before ingestion. In this respect these compounds are not superior to sodium salicylate which does not produce direct gastric irritation when properly guarded by a bicarbonate. The taste however is much less objectionable than that of the simpler salicylate salts.

Compounds which hydrolyze to produce salicylic acid may be of the following types

- 1 Simple salts of salicylic acid e g sodium salicylate
- 2 Acyl esters of salicylic acid involving the phenolic hydroxyl group e g acetylsalicylic acid.
- 3 Alkyl and aryl esters of salicylic acid involving the carboxylic group e g methyl salicylate and phenyl salicylate respectively

The acyl derivatives (acetylsalicylic acid type) possess a higher analgesic and antipyretic action than simple salicylate salts.

The alkyl esters (methyl salicylate type) are absorbed readily from the skin and are therefore better for external use than simpler salicylates.

The aryl esters (phenyl salicylate type) hydrolyze to active phenols and salicylic acid. They have been used for intestinal antiseptics but are of doubtful value.

1 EQUIVALENTS OF 100 PARTS OF VARIOUS SALICYLIC ACID
DERIVATIVES IN TERMS OF SALICYLIC ACID
AND SODIUM SALICYLATE

100 Parts of	Equivalent Parts of Salicylic Acid	Equivalent Parts of Sodium Salicylate
Salysal	106.2	124
Salicylic acid	100	116
Sodium salicylate	86	100
Acetylsalicylic acid	77	89
Salicyl ethyl carbonate	77	89
Novaspirin	67	72

Acid Derivatives (Acyl Esters) of Salicylic Acid

These are employed as analgesics and antipyretics in rheumatic conditions and in colds, neuralgias, etc. Their analgesic effects surpass those of sodium salicylate. Their acid character causes some local irritation which may be quite marked when large doses are taken. The promiscuous use of acetylsalicylic acid (aspirin) by the laity especially for the relief of headache has led to rather severe poisoning, the chief symptoms being edema of the lips, tongue, eyelids, nose, or of the entire face; also urticarial rashes, vertigo, nausea, and sometimes cyanosis. Atopic asthmatic persons are especially susceptible to these effects of acetylsalicylic acid and several deaths have been reported from its use by such individuals.

ACETYLSALICYLIC ACID—Aspirin—When dried over sulfuric acid for 5 hours contains not less than 99.5 per cent of $\text{HC}_7\text{H}_7\text{O}_2 \cdot \text{C}_7\text{H}_7\text{O}_2$. *U. S. P.*

For description and standards see the U. S. Pharmacopoeia under Acetylsalicylic Acid.

Actions and Uses—See preceding article Acid Derivatives (Acyl Esters) of Salicylic Acid.

Dosage—From 0.3 to 1 Gm. repeated once in three hours until symptoms of salicylism (ringing in the ears, etc.) are noted. It may be administered in the form of powder; this may be administered by placing it on the tongue and taking a swallow of water. The powder should be dispensed in wax paper.

SALYSAL—The salicylic ester of salicylic acid— $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{COO} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$.

Actions and Uses—See preceding article Acid Derivatives of Salicylic Acid. Being insoluble in water and dilute acids.

salysal is said to be relatively free from disagreeable taste and local irritating action

Dosage—From 0.3 to 0.6 Gm two to three times a day. Salysal is approximately twice as active therapeutically as sodium salicylate and may be employed in one-half the dosage of the latter drug.

Tests and Standards—

Salysal occurs as a white, odorless, tasteless stable crystalline powder. It is soluble in alcohol, ether and solutions of alkalis, slightly soluble in benzene and insoluble in water and dilute acids. Salysal melts at 147 to 149 C.

Dissolve 0.5 Gm of salysal in 5 cc of sulfuric acid; no more than a faint yellow color appears (*readily carbonizable substances*). Shake 1 Gm of salysal with 25 cc of cold water; filter and add 1 cc of ferric chloride solution; no violet color appears (*free salicylic acid*). Dissolve 0.5 Gm of salysal in 10 cc of alcohol and add 1 cc of dilute nitric acid and 1 cc of silver nitrate solution; no precipitate is produced (*chlorides*). Incinerate about 2 Gm of salysal, accurately weighed; the ash does not exceed 0.25 per cent. Dry about 1 Gm of salysal accurately weighed to constant weight at 100 C; the loss in weight does not exceed 0.5 per cent.

Transfer about 0.5 Gm of salysal previously dried and accurately weighed to a 200 cc flask and add 50 cc of diluted alcohol which has been previously neutralized to phenolphthalein. Add to this solution 10 cc of 10% sodium hydroxide solution. Boil for one hour, cool and add 10 cc of 10% sodium hydroxide solution. The solution should be pink with tenth normal sodium hydroxide solution.

RARE CHEMICALS, INC.

Salysal (Powder): bulk

Tablets Salysal: 0.325 Gm

U. S. Patent 922,995 (May 25, 1909, expired). The firm has relinquished Trademark rights to the name.

Alkyl Esters of Salicylic Acid

These act somewhat more slowly, but otherwise as efficiently as sodium salicylate. They are for the most part saponified in the intestines, but some may be absorbed unchanged. They frequently cause somewhat more local irritation. They are also quite well absorbed from the skin, and may, therefore, be applied externally, usually dissolved in olive oil. Methyl salicylate is official in the U. S. Pharmacopoeia.

ETHYL SALICYLATE—Aethylis Salicylas— $C_6H_5OCH_2CH_3$ COO (C_2H_5)—The salicylic acid ester of ethyl alcohol analogous to methyl salicylate (oil of wintergreen).

Actions and Uses—Ethyl salicylate has the same action as methyl salicylate, but is said to be less irritant and less toxic.

Dosage—From 0.3 to 0.6 cc three or four times a day.

Tests and Standards—

Ethyl Salicylate is a transparent colorless volatile liquid possessing a pleasant characteristic odor and taste. Its specific gravity is 1.132.

at 20 C and it boils at from 230 to 232 C It is insoluble in water but soluble in alcohol

PARKE, DAVIS & COMPANY

Capsules Sal-Ethyl: 03 cc

U S Trademark 92,115

SAL-ETHYL CARBONATE—The carbonic acid ester of ethyl salicylate—Salicylic ethyl ester carbonate— $\text{O C}(\text{OC}_2\text{H}_5\text{COOC}_2\text{H}_5)_2$

Actions and Uses—Sal-ethyl carbonate provides the antipyretic and analgesic effects of the salicylates It is relatively insoluble in water and in the acid secretions of the stomach

granulocytopenia in occasional individuals

Dosage—Sal-ethyl carbonate and tablets sal ethyl carbonate with aminopyrine may be given in dosages ranging from 03 to 1 Gm three or four times daily, according to the individual requirements

Tests and Standards.—

Sal ethyl carbonate occurs as white odorless and tasteless crystals It is almost insoluble in water and diluted hydrochloric acid It is slightly soluble in ether and alcohol but readily soluble in chloroform and acetone It melts between 96 and 99 C

Transfer about 2 Gm of sal ethyl carbonate to a test tube add 5 cc of half normal alcoholic potassium hydroxide and heat on the steam bath for five minutes the product dissolves and the formation of a precipitate follows cool decant the supernatant liquid add 6 per cent acetic acid to the precipitate, it effervesces, add an equal volume of water to the decanted liquid a colorless oil separates having the odor of ethyl salicylate Transfer about 1 Gm of sal ethyl carbonate to an Erlenmeyer flask add 20 cc of normal sodium hydroxide 20 cc of alcohol and boil under a reflux condenser for thirty minutes, cool acidify the solution by addition of diluted sulfuric acid, extract the solution with 20 cc of ether filter the ether, evaporate to dryness the residue responds to qualitative tests for salicylic acid

Dissolve about 05 Gm of sal ethyl carbonate in 10 cc of sulfuric acid the solution remains colorless for five minutes (*readily carbonizable substances*) Transfer about 05 Gm of sal ethyl carbonate to a test tube add 10 cc of water and a few drops of ferric chloride solution no blue color develops (*salicylic acid*)

Transfer about 1 Gm of sal ethyl carbonate accurately weighed to an Erlenmeyer flask, add 40 cc of half normal alcoholic potassium hydroxide boil under a reflux condenser on the steam bath for three hours wash the condenser and add the washings to the flask remove the alcohol by evaporating to about one third the volume adding 50 cc of water and evaporating to about 15 cc transfer the solution to a 250 cc volumetric flask, make up to volume by addition of water Transfer a 25 cc aliquot to an Erlenmeyer flask and test the solution according to the method for total salicylate described in the A O A C Manual third edition page 446 Iodine Method paragraph 24 the

weight of the tetraiodophenylene quinone multiplied by 0.5203 and by the aliquot factor is equivalent to not less than 98.5 per cent nor more than 100.5 per cent of the sample taken. Transfer about 1 Gm of sal-ethyl carbonate, accurately weighed, to a tared weighing bottle, heat in an oven at 100 C. for one hour, cool in a desiccator and weigh; the loss in weight is not greater than 1 per cent. Transfer about 0.5 Gm of sal-ethyl carbonate, accurately weighed, to a platinum dish and ignite; the ash is not more than 0.2 per cent.

PARKE, DAVIS & COMPANY

Sal-Ethyl Carbonate (*Powder*); bulk

Tablets Sal-Ethyl Carbonate: 0.325 Gm

Tablets Sal-Ethyl Carbonate with Aminopyrine. Each tablet contains sal-ethyl carbonate 0.23 Gm and aminopyrine U. S. P. 0.1 Gm.

U. S. Trademark 92,115

CHAPTER III

ANESTHETICS

Local Anesthetics

There are three general groups of drugs used for the production of local anesthesia (1) those which cause anesthesia through the production of cold such as ether ethyl chloride and methyl chloride, (2) certain protoplasmic poisons as quinine and (3) those having a specific effect on sensory nerves or their endings cocaine being the type of this class

The drugs listed below belong in general to the third class. They have been introduced with the object of finding substances less toxic and more stable and less injurious to the tissues than cocaine. Their anesthetic power is also as a rule somewhat less than that of cocaine and some of them present the usually undesirable effect of dilating the blood vessels or at least of not constricting them as does cocaine and are therefore almost always employed in conjunction with epinephrine. The most important are based on the discovery that the local anesthetic action of cocaine is due to the radical of benzoic acid in combination with a nitrogen containing basic group. The simplest of these compounds ethylaminobenzoate (benzo-

para aminobenzoic acid
ethyl ester of hydroxy

These are too weak
useful for hypodermic
injection (See Slightly
chloride is the hydro

chloride of a compound of para aminobenzoic acid with diethyl aminoethyl alcohol its salts are readily soluble in water. Only those local anesthetics of relatively low toxicity should be injected or others where very small amounts are required.

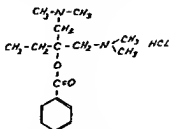
The local anesthetics can be used with safety in nearly all suitable cases if precautions are observed but extreme caution is imperative when any local anesthetic is injected into the traumatized urethra or under conditions in which trauma is likely to occur. The details of dosage of any of the several local anesthetics should be learned with reference to various modifications for different applications.

Soluble Local Anesthetics

ALYPIN HYDROCHLORIDE—Amydricaine Hydrochloride—The hydrochloride of 2 benzoxy 2 dimethylamino methyl 1 dimethylaminobutane

Actions and Uses—Alypin hydrochloride is a local anesthetic claimed to be equal to cocaine but is not a mydriatic. It is said not to produce disturbance of accommodation and to be

less toxic than cocaine, but the evidence as to the relative toxicity of alypin hydrochloride and cocaine is rather conflicting. Death was reported in one case from the injection of about 12 cc of a 4 per cent solution into the urethra; severe poisoning has resulted from smaller amounts.



Dosage—Alypin hydrochloride is used in solutions the strength of which is about the same as that of cocaine hydrochloride, in rhinolaryngology 1 per cent (see caution under y), 0.5 to 2 per cent, and

y be sterilized by boiling the required amount of water for 10 minutes in a test tube stoppered with cotton, the drug is then added and the boiling continued over a small flame for another minute. Solutions should be freshly prepared. Epinephrine preparations may be added when a vasoconstrictor effect is desired.

Tests and Standards—

Alypin hydrochloride is a white crystalline powder of less bitter and hygroscopic. It is very soluble in water, freely soluble in alcohol and chloroform, insoluble in ether. Its aqueous solutions are neutral and are not rendered turbid on the addition of sodium bicarbonate solution in moderate quantities. Its aqueous solutions may be sterilized by boiling for a period not exceeding five minutes without decomposition. Two and four per cent aqueous solutions are quite stable but weaker solutions are likely to become moldy. It should be protected from the air in well stoppered containers. With the aqueous solution (1 in 100) potassium dichromate solution produces an orange yellow crystalline precipitate which is soluble in hydrochloric acid. Potassium permanganate solution produces a violet crystalline precipitate which turns brown on standing. An aqueous solution of alypin hydrochloride (1 in 100) gives precipitates with potassium mercuric iodide solution, iodine solution, picric acid solution, gold chloride solution and many other alkaloidal reagents; it also gives precipitates with potassium iodide solution and mercuric chloride solution. Mix 0.1 Gm. of alypin hydrochloride with 1 cc. of sulfuric acid, warm the mixture to 100 C. for five minutes and carefully add 2 cc. of water. (Caution) The odor of ethylbenzoate is developed. On cooling the mixture, crystals separate which are dissolved on adding 2 cc. of alcohol.

Dry about 1 Gm. of alypin hydrochloride accurately weighed to constant weight at 100 C. the loss should not exceed 2 per cent.

Incinerate about 0.5 Gm. of alypin hydrochloride accurately weighed the ash does not exceed 0.1 per cent.

WINTHROP CHEMICAL COMPANY, INC

Alypin Hydrochloride (Powder). bulk

Tablets Alypin Hydrochloride. 22 mg

U S patent 808 748 (Jan 2 1906, expired) U S trademark 44 608

AMYLSINE HYDROCHLORIDE—Amylcaine—Mono-
 " amyl aminoethyl *p* aminobenzoate hydrochloride — $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{COO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{HCl}$ (Formerly known as Amylcaine [āmyl cāine] Hydrochloride, the name having been changed to avoid confusion with the official preparation of British Pharmacopoeia)

Actions and Uses—The actions of amylsine hydrochloride resemble those of cocaine hydrochloride, but it does not cause mydriasis when the solution is dropped into the eye. In the present state of our knowledge its use should be restricted to the production of corneal anesthesia in those cases in which mydriasis is not desired. The toxicity varies rather widely with the species and with the mode of administration. The anesthesia is induced promptly with little smarting, it does not increase intraocular tension.

Dosage—A 2 per cent solution is used in ophthalmology when mydriasis is not desired, 1 or 2 drops being usually sufficient.

Tests and Standards—

Amylsine hydrochloride occurs as a fine white, odorless powder which, when applied to the tongue possesses a bitter taste followed by a sense of numbness. It is soluble in water sparingly soluble in ethanol and insoluble in ether benzene and chloroform. An aqueous solution is acid to litmus. The free base separates as a solid from amylsine hydrochloride solutions on the addition of sodium hydroxide or carbonate solutions but not with sodium bicarbonate solution. Amylsine hydrochloride occurs in dimorphic forms. The form which crystallizes from high boiling solvents melts at 176 C. while the one crystallized at lower temperatures melts at 153.5 C., the free base melts at 65 C.

Identification—Add 0.1 Gm. of amylsine hydrochloride to a solution of 0.1 Gm. of amylsine hydrochloride in 5 cc. of water add 2 drops of sulfuric acid and 1 cc. of a saturated solution of sodium nitrite and heat to 50 C. a yellow oil separates (distinction from procaine butyn, cocaine, tincture of cocaine and pontocaine). Dissolve 0.1 Gm. of amylsine hydrochloride in 1 cc. of sulfuric acid the solution is colorless (readily carbonizable substances). Saturate a solution of 0.1 Gm. in 10 cc. of water with hydrogen sulfide no coloration or precipitation occurs (salts of heavy metals).

Transfer about 0.5 Gm of amylsine hydrochloride, accurately weighed to a tared platinum dish and dry at 100 C for six hours. The loss in weight does not exceed 3 per cent. Incinerate about 0.5 Gm of amylsine hydrochloride accurately weighed. The ash does not exceed 0.1 per cent. Transfer a sample of amylsine hydrochloride previously dried and accurately weighed to a Kjeldahl flask and digest with sulfuric acid in the presence of 0.1 Gm of selenium. Dilute, make alkaline with sodium hydroxide solution, distil into standard acid and titrate the excess acid with standard alkali. The nitrogen content is not greater than 9.8 nor less than 9.4 per cent. Transfer about 0.5 Gm of amylsine hydrochloride previously dried and accurately weighed to a 250 cc beaker and dissolve in 100 cc of water. Heat to boiling and add 10 cc of nitric acid and 20 cc of a silver nitrate solution. Digest on the steam bath for three hours, filter, wash, dry and weigh the precipitate. The chloride content is not greater than 12.5 nor less than 12.0 per cent.

NOVOCOL CHEMICAL MFG CO., INC

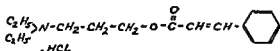
Amylsine Hydrochloride (Powder) 5 Gm vials and 30 cc bottles

Amylsine Hydrochloride Solution 2% 30 cc bottles

Amylsine Hydrochloride Solution 4% 30 cc bottles

U S Patent 2,139,818 (Dec 13 1938 expires 1955) U S trade mark 404,009

APOTHESINE HYDROCHLORIDE— γ diethylamino propyl cinnamate hydrochloride. The hydrochloride of a condensation product prepared by the action of cinnamoyl chloride on γ diethylaminopropanol.



Actions and Uses—Apothesine hydrochloride is a local anesthetic of the procaine rather than the cocaine type that is it belongs to that type which while effective for injection anesthesia (especially when combined with epinephrine) is relatively inefficient when applied to mucous membranes. It is rather slower in action than procaine hydrochloride. Its absolute toxicity is about equal to that of cocaine but about twice that of procaine hydrochloride (as 20 is to 40). When injected somewhat stronger solutions are required than are necessary with procaine hydrochloride or especially with cocaine but with adequate concentrations the anesthesia is just as complete. It is employed for infiltration injection nerve blocking intraspinal injection pressure anesthesia and oral surgery as a palliative.

measure for its local anesthetic effect. Apothesine hydrochloride solutions are not injured by boiling. (See caution under the general article, Local Anesthetics.)

Dosage—As a local anesthetic 0.5 to 2 per cent solution generally with epinephrine hydrochloride in sterile water or physiologic solution of sodium chloride. For spinal anesthesia 2 cc. of a 4 per cent solution.

Tests and Standards—

Apothesine hydrochloride occurs in white masses which are composed of small white crystals, practically odorless and stable in air, faintly bitter, but producing a sense of numbness of the tongue. It is soluble in water and in alcohol, slightly soluble in acetone or ether. Its aqueous solution is neutral to litmus paper. The solution is stable. Aqueous solutions of apothesine hydrochloride produce precipitates with the alkali hydroxides and their carbonates (the precipitate formed with sodium bicarbonate is soluble in an excess of the reagent) and with the usual alkaloid reagents. The free base apothesine occurs as an oil, when heated with strong sodium hydroxide it is decomposed to diethylaminopropylalcohol and sodium cinnamate.

Apothesine hydrochloride melts at 136°C.

An aqueous solution of apothesine hydrochloride gives with silver nitrate solution a white precipitate which is soluble in an excess of ammonia water.

Dissolve about 0.1 Gm. of apothesine hydrochloride in 5 cc. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent) and mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent); a white precipitate is formed (distinction from *ethyl aminobenzoate* which gives a cherry red color in a solution containing undissolved benzocaine and from *procaine hydrochloride* which gives a scarlet precipitate).

Add a few drops of gold chloride solution to an aqueous solution of apothesine hydrochloride (1 in 100); a lemon yellow precipitate is produced (distinction from *ethyl aminobenzoate* and *procaine hydrochloride* which form brown precipitates).

Dissolve about 0.1 Gm. of apothesine hydrochloride in 5 cc. of water, add 3 drops of diluted sulfuric acid and 5 drops of potassium permanganate solution; the violet color of the latter disappears immediately (distinction from *cocaine* which gives a violet precipitate).

Dissolve 0.1 Gm. of apothesine hydrochloride in 1 cc. of sulfuric acid; the solution remains colorless (*organic impurities*).

Dissolve 0.1 Gm. of apothesine hydrochloride in 10 cc. of water and saturate the solution with hydrogen sulfide; no coloration or precipitation is produced (*salts of heavy metals*).

Incinerate about 0.5 Gm. of apothesine hydrochloride accurately weighed; not more than 0.1 per cent of residue remains.

PARKE, DAVIS & COMPANY

Apothesine Hydrochloride Solution, 1½% Each 100 cc. contains 1.5 Gm. of apothesine hydrochloride and 0.5 Gm. of chlorobutanol as a preservative.

Apothesine Hydrochloride Hypodermic Tablets 80 mg.

Apothesine Hydrochloride and Adrenalin Hypodermic Tablets 0.3 Gm. Each tablet contains apothesine hydrochloride 0.3 Gm. and epinephrine hydrochloride 0.3 mg. and not more than 0.3 mg. of sodium bisulphite.

Apothesine Hydrochloride and Adrenalin Hypodermic Tablets 39 mg Each tablet contains apothesine hydrochloride 39 mg and epinephrine hydrochloride 0.04 mg and not more than 0.3 mg of sodium bisulfite

U. S. patents 1,193,634 1,193,649 1,193,650 and 1,193,651 (Aug. 8 1916, expired)

BENZYL ALCOHOL—*Alcohol Benzylicum*.—Phenyl methylol— $C_6H_5CH_2OH$ —An aromatic alcohol occurring as an ester in tolu and other balsams the product on the market is produced synthetically

Actions and Uses—Benzyl alcohol is used as a local anesthetic by injection and by application to mucous membranes. It is practically nonirritant and nontoxic in the ordinary concentrations and doses. (See caution under the general article Local Anesthetics)

Dosage—Benzyl alcohol is usually used in the form of a 1 to 4 per cent solution in water or physiological solution of sodium chloride. Such solutions may be sterilized by boiling without danger of decomposition. Pure benzyl alcohol is markedly antiseptic. The technique of injection is the same as for other local anesthetics. It is applied against pruritus as a 10 per cent ointment, in lard, or as a lotion of equal parts of benzyl alcohol and water.

Tests and Standards—

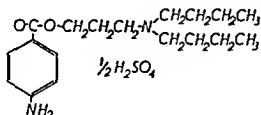
Benzyl alcohol is a colorless liquid with a faint aromatic odor and a sharp burning taste. When placed on the tongue it produces numbness even if only a small quantity is used. It is soluble 1 cc in 25 cc of water and miscible in all proportions with alcohol, ether and chloroform. One volume of benzyl alcohol should dissolve in 1.5 volumes of 50 per cent alcohol. Benzyl alcohol boils without decomposition between 200 and 206°C. When ignited it burns with a smoky flame. It has a specific gravity of from 1.040 to 1.050 at 15°C and 1.032 to 1.042 at 25°C.

Benzyl alcohol is neutral to litmus. If 2 or 3 drops are added to a strong solution of potassium permanganate acidulated with sulfuric acid, rapid oxidation takes place and the odor of benzaldehyde is plainly evident. On heating the mixture further oxidation takes place and then by adding dilute sulfuric acid and decolorizing the mixture with hydrogen dioxide benzoic acid may be obtained by extraction with ether. Wind the end of a copper wire to a spiral about 6.3 mm (one fourth inch) in diameter and length and hold this spiral in a nonluminous flame until no green coloration is imparted to the flame; dip the spiral into the benzyl alcohol to be tested and burn off the adhering liquid outside the flame; place the nonluminous flame against a dark background and hold the loop in the right or left margin of the flame; not even a transient green coloration should be imparted to the flame (*limit of chlorine compounds*). If 5 cc is shaken with 5 cc of sodium hydroxide solution (5 per cent) and allowed to stand one hour no yellow color should appear in the aqueous layer (*aldehyde*).

Ten cc of benzyl alcohol should leave no weighable residue on evaporation and heating until all carbon is burned away.

SPYDEL CHEMICAL COMPANY

Benzyl Alcohol • bulk

BUTACAINE SULFATE—U S P—Butyn Sulfate

For description and standards see the U S Pharmacopeia under Butacaine Sulfate

Actions and Uses—Butacaine sulfate is a local anesthetic proposed as a substitute for cocaine particularly in surface anesthesia as for the eye nose and throat. It has the special advantage of acting through intact mucosae about as effectively as cocaine. On the normal human eye a 1 per cent solution of butacaine sulfate is as effective as a 1 per cent solution of phenacaine hydrochloride (holocaine), and more efficient than a 1 per cent solution of cocaine hydrochloride or a 1 per cent solution of eucaine. The instillation of butacaine sulfate solutions often produces congestion of the conjunctiva but this does not appear to be of practical significance.

When butacaine sulfate is injected hypodermically into albino rats the toxicity is two and one half times that of cocaine but the lethal dose (injected intravenously into cats) is about equal to that of cocaine. Pharmacologic study indicates that butacaine sulfate may take the place of cocaine in whole or in part for surface anesthesia of mucous membranes and that it may be superior for this purpose, especially for use in the eye to other anesthetics for the reason that it can be used in materially lower concentrations (presumably because of more prompt absorption). On the other hand it does not appear promising for injection anesthesia or for spinal anesthesia since its toxicity is materially greater than that of procaine hydrochloride, but butacaine sulfate is used for injection anesthesia, in concentrations of 0.1 to 0.4 per cent.

A committee of the Section of Ophthalmology of the American Medical Association (*J A M A* 78:343 [Feb 4] 1922) reported the successful use of butacaine sulfate in practically all operations on the eye and in some operations on the nose and throat. The committee concluded that butacaine sulfate is more powerful than cocaine, a smaller quantity being required that it acts more rapidly than cocaine and that

the action is more prolonged. So far as the experiences of the committee go butacaine sulfate in the quantity required is less toxic than cocaine. The committee found butacaine sulfate superior to cocaine in that it produces no drying of the tissues and no change in the size of the pupil and that it has no ischemic effect.

Dosage—For ophthalmologic work butacaine sulfate is generally used in 2 per cent solutions. A single application produces within one minute an anesthesia sufficient to permit the removal of superficially placed foreign bodies, the application of irritant astringents and the use of the tonometer. Four instillations three minutes apart permit operative work within five minutes after the last instillation producing an anesthesia sufficient to perform all of the commoner operations on the eye. For topical use in nose and throat work a 2 per cent solution is usually employed. Butacaine sulfate solutions may be sterilized by boiling. (See caution under the general article Local Anesthetics.)

ABBOTT LABORATORIES

Butyn Sulfate (Crystals) bulk

Butyn Sulfate Solution 2 per Cent

Butyn Sulfate Tablets 0.2 Gm

Butyn Sulfate and Epinephrine Hypodermic Tablets
Butacaine sulfate 10 mg epinephrine hydrochloride 0.032 mg
sodium bisulfite 16 mg

Ophthalmic Ointment Butyn Sulfate 2% and Metaphen
1:3000 contains 2 per cent of butacaine sulfate with metaphen
1:3000 in a base of petrolatum 75 per cent and wool fat
25 per cent

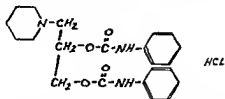
U. S. patent 1,358,752 (Nov. 16, 1920 exp. red.) 1,676,470 (July 10, 1928 exp. red.) U. S. trademark 147,893

MANHATTAN EYE SALVE COMPANY, INC.

Butyn Sulfate Ointment 1% Butacaine sulfate 1 per cent water 1 per cent wool fat 5 per cent and petrolatum sterile 93 per cent. Put up in collapsible tubes for application to the eye.

DIOTHANE HYDROCHLORIDE—Diothane—Piperidinopropanediol *d,l*-phenylurethane hydrochloride— $C_8H_{13}NCH_2CH(OCONHC_6H_5)CH_2(OCONHC_6H_5)HCl$ —The hydrochloride of the base piperidino propanediol *d,l*-phenylurethane

obtained by combining piperidine and glycerol monochlorohydrin in the presence of an alkali, and reacting the piperidinopropanoidol with phenyl isocyanate



Actions and Uses—Nearly similar to those of cocaine, but it is claimed that the anesthesia lasts somewhat longer than that induced by corresponding doses of cocaine hydrochloride or procaine hydrochloride. Its toxicity by intravenous injection is about three times that of procaine hydrochloride and hence it should not be injected except in small amounts. Diothane hydrochloride is also available as a cream for topical use as a surface anesthetic and analgesic. It is claimed to be useful for the relief of surface pain and irritation in abrasions of the skin and mucous membranes, following hemorrhoidectomy and for the relief of pain in nonoperable cases of hemorrhoids.

Solutions of diethane hydrochloride prepared extemporaneously should be used promptly, since such solutions usually contain traces of alkali and are thereby subject to precipitation

Dosage—A 1 per cent solution is applied to mucous membranes, 0.5 per cent solutions may be injected. (See caution under the general article, Local Anesthetics) The cream is rubbed into the affected area a second thin coating applied and covered with dressings within ten or fifteen minutes.

Tests and Standards—

Diothane hydrochloride occurs as a fine white crystalline, odorless powder when applied to the tongue it produces a bitter taste followed by a sense of numbness stable in air at ordinary temperatures slightly soluble in water acetone and ethyl acetate, soluble in alcohol insoluble in benzene and ether Its aqueous solution (1 in 100) is faintly acid to litmus Diothane hydrochloride melts at 195 to 200 C with decomposition From aqueous solutions alkali carbonates and hydroxides precipitate the free base as a colorless oil which does not solidify under ordinary conditions

	D ₁	D ₂	D ₃	D ₄	D ₅	D ₆	D ₇	D ₈	D ₉	D ₁₀	D ₁₁	D ₁₂	D ₁₃	D ₁₄	D ₁₅	D ₁₆	D ₁₇	D ₁₈	D ₁₉	D ₂₀	D ₂₁	D ₂₂	D ₂₃	D ₂₄	D ₂₅	D ₂₆	D ₂₇	D ₂₈	D ₂₉	D ₃₀	D ₃₁	D ₃₂	D ₃₃	D ₃₄	D ₃₅	D ₃₆	D ₃₇	D ₃₈	D ₃₉	D ₄₀	D ₄₁	D ₄₂	D ₄₃	D ₄₄	D ₄₅	D ₄₆	D ₄₇	D ₄₈	D ₄₉	D ₅₀	D ₅₁	D ₅₂	D ₅₃	D ₅₄	D ₅₅	D ₅₆	D ₅₇	D ₅₈	D ₅₉	D ₆₀	D ₆₁	D ₆₂	D ₆₃	D ₆₄	D ₆₅	D ₆₆	D ₆₇	D ₆₈	D ₆₉	D ₇₀	D ₇₁	D ₇₂	D ₇₃	D ₇₄	D ₇₅	D ₇₆	D ₇₇	D ₇₈	D ₇₉	D ₈₀	D ₈₁	D ₈₂	D ₈₃	D ₈₄	D ₈₅	D ₈₆	D ₈₇	D ₈₈	D ₈₉	D ₉₀	D ₉₁	D ₉₂	D ₉₃	D ₉₄	D ₉₅	D ₉₆	D ₉₇	D ₉₈	D ₉₉	D ₁₀₀	D ₁₀₁	D ₁₀₂	D ₁₀₃	D ₁₀₄	D ₁₀₅	D ₁₀₆	D ₁₀₇	D ₁₀₈	D ₁₀₉	D ₁₁₀	D ₁₁₁	D ₁₁₂	D ₁₁₃	D ₁₁₄	D ₁₁₅	D ₁₁₆	D ₁₁₇	D ₁₁₈	D ₁₁₉	D ₁₂₀	D ₁₂₁	D ₁₂₂	D ₁₂₃	D ₁₂₄	D ₁₂₅	D ₁₂₆	D ₁₂₇	D ₁₂₈	D ₁₂₉	D ₁₃₀	D ₁₃₁	D ₁₃₂	D ₁₃₃	D ₁₃₄	D ₁₃₅	D ₁₃₆	D ₁₃₇	D ₁₃₈	D ₁₃₉	D ₁₄₀	D ₁₄₁	D ₁₄₂	D ₁₄₃	D ₁₄₄	D ₁₄₅	D ₁₄₆	D ₁₄₇	D ₁₄₈	D ₁₄₉	D ₁₅₀	D ₁₅₁	D ₁₅₂	D ₁₅₃	D ₁₅₄	D ₁₅₅	D ₁₅₆	D ₁₅₇	D ₁₅₈	D ₁₅₉	D ₁₆₀	D ₁₆₁	D ₁₆₂	D ₁₆₃	D ₁₆₄	D ₁₆₅	D ₁₆₆	D ₁₆₇	D ₁₆₈	D ₁₆₉	D ₁₇₀	D ₁₇₁	D ₁₇₂	D ₁₇₃	D ₁₇₄	D ₁₇₅	D ₁₇₆	D ₁₇₇	D ₁₇₈	D ₁₇₉	D ₁₈₀	D ₁₈₁	D ₁₈₂	D ₁₈₃	D ₁₈₄	D ₁₈₅	D ₁₈₆	D ₁₈₇	D ₁₈₈	D ₁₈₉	D ₁₉₀	D ₁₉₁	D ₁₉₂	D ₁₉₃	D ₁₉₄	D ₁₉₅	D ₁₉₆	D ₁₉₇	D ₁₉₈	D ₁₉₉	D ₂₀₀	D ₂₀₁	D ₂₀₂	D ₂₀₃	D ₂₀₄	D ₂₀₅	D ₂₀₆	D ₂₀₇	D ₂₀₈	D ₂₀₉	D ₂₁₀	D ₂₁₁	D ₂₁₂	D ₂₁₃	D ₂₁₄	D ₂₁₅	D ₂₁₆	D ₂₁₇	D ₂₁₈	D ₂₁₉	D ₂₂₀	D ₂₂₁	D ₂₂₂	D ₂₂₃	D ₂₂₄	D ₂₂₅	D ₂₂₆	D ₂₂₇	D ₂₂₈	D ₂₂₉	D ₂₃₀	D ₂₃₁	D ₂₃₂	D ₂₃₃	D ₂₃₄	D ₂₃₅	D ₂₃₆	D ₂₃₇	D ₂₃₈	D ₂₃₉	D ₂₄₀	D ₂₄₁	D ₂₄₂	D ₂₄₃	D ₂₄₄	D ₂₄₅	D ₂₄₆	D ₂₄₇	D ₂₄₈	D ₂₄₉	D ₂₅₀	D ₂₅₁	D ₂₅₂	D ₂₅₃	D ₂₅₄	D ₂₅₅	D ₂₅₆	D ₂₅₇	D ₂₅₈	D ₂₅₉	D ₂₆₀	D ₂₆₁	D ₂₆₂	D ₂₆₃	D ₂₆₄	D ₂₆₅	D ₂₆₆	D ₂₆₇	D ₂₆₈	D ₂₆₉	D ₂₇₀	D ₂₇₁	D ₂₇₂	D ₂₇₃	D ₂₇₄	D ₂₇₅	D ₂₇₆	D ₂₇₇	D ₂₇₈	D ₂₇₉	D ₂₈₀	D ₂₈₁	D ₂₈₂	D ₂₈₃	D ₂₈₄	D ₂₈₅	D ₂₈₆	D ₂₈₇	D ₂₈₈	D ₂₈₉	D ₂₉₀	D ₂₉₁	D ₂₉₂	D ₂₉₃	D ₂₉₄	D ₂₉₅	D ₂₉₆	D ₂₉₇	D ₂₉₈	D ₂₉₉	D ₃₀₀	D ₃₀₁	D ₃₀₂	D ₃₀₃	D ₃₀₄	D ₃₀₅	D ₃₀₆	D ₃₀₇	D ₃₀₈	D ₃₀₉	D ₃₁₀	D ₃₁₁	D ₃₁₂	D ₃₁₃	D ₃₁₄	D ₃₁₅	D ₃₁₆	D ₃₁₇	D ₃₁₈	D ₃₁₉	D ₃₂₀	D ₃₂₁	D ₃₂₂	D
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Gm of diothane hydrochloride in 1 cc of sulfuric acid the solution is colorless (*readily carbonizable substances*) Saturate about 0.1 Gm of diothane hydrochloride dissolved in 10 cc of water with hydrogen sulfide—no coloration or precipitation results (*salts of heavy metals*)

Dry about 0.5 Gm of diothane hydrochloride, accurately weighed at 100 C for six hours the loss in weight does not exceed 0.5 per cent Incinerate about 0.5 Gm of diothane hydrochloride, accurately weighed the residue is not more than 0.1 per cent Transfer about 0.3 Gm of diothane hydrochloride, accurately weighed, to a 500 cc Kjeldahl flask, and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22 the percentage of nitrogen corresponds to not less than 9.5 per cent, nor more than 9.8 per cent when calculated to the dried substance Dissolve about 0.25 Gm of diothane hydrochloride, accurately weighed, in 25 cc of water, by warming, and transfer to a suitable Squibb separatory funnel rinse twice using about 10 cc of water, followed by the addition of 3 cc of a diluted ammonia water (one part of ammonia water and ten parts of water) extract with four successive portions of ether using 20 cc each, filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air, dissolve the oily residue in about 25 cc of previously neutralized alcohol, warm slightly, add 10 cc of tenth normal hydrochloric acid solution, followed by the addition of 10 cc of water determine the excess of acid by titration with tenth normal sodium hydroxide solution, using bromphenol blue as an indicator the amount of tenth normal hydrochloric acid consumed corresponds to not less than 80.5 per cent

nitric acid and 25 cc of silver nitrate solution, subsequently boil with continuous stirring and allow to cool in a dark place Collect the precipitate of silver chloride on a Gooch crucible wash with diluted nitric acid and water, followed by alcohol and ether, finally dry to constant weight at 105 C, the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 8.35 per cent, nor more than 8.45 per cent when calculated to the dried substance

THE WM S MERRELL COMPANY

Diothane Hydrochloride (Crystals): Bulk.

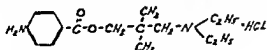
Diothane Hydrochloride 0.5% in Solution of Sodium Chloride 0.6%: 6 cc ampuls.

Diothane Hydrochloride Solution, 1%: A solution of diothane hydrochloride, 1 per cent, in distilled water

U S patent 2,004,132 (June 11, 1935, expires 1952) U S trademark 296,850

* aminobenzoyl-
de — γ -diethyl-
hydrochloride —
The base of

larocaine belongs to the procaine type. It differs from procaine in having a propanol group instead of the ethanol group and has two methyl groups attached to the former.



Actions and Uses—Larocaine hydrochloride acts as a surface, as well as an infiltration, anesthetic and compares quite favorably in both fields with either cocaine or procaine. Larocaine hydrochloride is quick in action and produces anesthesia of a somewhat longer duration than cocaine or procaine. The average duration of conduction anesthesia is from three to five hours. Larocaine hydrochloride is non narcotic and non habit forming.

Dosage—For corneal and conjunctival anesthesia, from 2 to 5 per cent solutions may be used. In otorhinolaryngology, 5 to 10 per cent solutions have been employed. From 0.75 to 1 per cent solutions are used in urology. For conduction anesthesia, 0.25 to 2 per cent solutions may be used. Solutions of larocaine hydrochloride may be sterilized by boiling for ten minutes. Epinephrine when desired may be added just prior to administration. Stock solutions should be kept in dark bottles. (See caution under the general article, Local Anesthetics.)

Tests and Standards—

Larocaine hydrochloride occurs as a fine white odorless crystalline powder. When applied to the tongue, it possesses a bitter taste followed by a sense of numbness, stable in air at ordinary temperatures. Freely soluble in water, soluble in alcohol, sparingly soluble in chloroform, insoluble in ether. Its aqueous solution is faintly acid to litmus. Larocaine hydrochloride melts at 196-197° C., with decomposition. From aqueous solutions alkali carbonates and hydroxides precipitate the free base as a colorless oil, which solidifies after a time at ordinary temperature.

described in Official and Tentative Methods of Analysis of the Association of
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etheral solution with 15 cc of water filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air, expose over sulfuric acid in a partially exhausted desiccator dissolve the oily residue in about 20 cc of previously neutralized alcohol warm slightly, add 12.5 cc of tenth normal hydrochloric acid solution followed by the addition of an equal volume of water, determine the excess of acid by titration with tenth normal sodium hydroxide solution, using methyl red as an indicator the amount of tenth normal hydrochloric acid solution consumed corresponds to not less than 87 per cent nor more than 89 per cent aminobenzoyldimethyldiethylamino propanol when calculated to the dried substance Transfer the ammoniacal aqueous portion from the immiscible solvent extraction to a 400 cc beaker and place on the steam bath for three hours add 100 cc of water, followed by the addition of 10 cc of nitric acid and 25 cc of silver nitrate solution, subsequently boil with continuous stirring and allow to cool in a dark place Collect the precipitate of silver chloride on a Gooch crucible, wash with diluted nitric acid and water followed by alcohol and ether, finally dry to constant weight at 105 C the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 11.5 per cent nor more than 11.7 per cent when calculated to the dried substance

HOFFMAN-LAROCHE, INC

Larocaine Hydrochloride (Powder), bulk

Tablets Larocaine Hydrochloride 0.25 Gm Each tablet contains larocaine hydrochloride, 0.25 Gm and boric acid, 25 mg

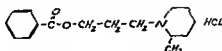
U S patent 1,824,676 (Sept. 22, 1931; expires 1948) U S trade mark 283,775

METYCAINE

methylpiperidino) pro

dino)-propylbenzoate

HCl—The base of metycaine hydrochloride differs from the base of procaine hydrochloride in having the basic nitrogen in a methylpiperidino ring instead of the dimethylamine, a propanol group in place of the ethanol group and in not having an amino group attached to the benzene ring. In addition, it possesses an asymmetric carbon atom and is optically inactive. Metycaine hydrochloride is therefore a racemic mixture of the hydrochlorides



Actions and Uses—Metycaine hydrochloride is a local anesthetic which produces prompt anesthesia either by subcutaneous injection or topical application to mucous membranes and similar

surfaces. Pharmacologic studies on animals indicate that its toxicity following subcutaneous injection is lower than that of cocaine and comparable to that of procaine, intravenously, it was found to be approximately three times as toxic as procaine.

Dosage—For application to the eye metycaine hydrochloride is used in 2 per cent solutions, for nose and throat, 2 to 10 per cent solutions are used, 1 to 4 per cent solutions have been used for urethral anesthesia, for infiltrative anesthesia in small areas, solutions of 0.5 to 1 per cent are generally used. (See caution under the general article, Local Anesthetics.)

Tests and Standards—

does not solidify at ordinary temperatures

Reaction) Dissolve about 0.1 Gm. of metycaine hydrochloride in 1 cc. of sulfuric acid; the solution is colorless (*readily carbonizable substances*). Dissolve about 0.5 Gm. in 50 cc. of water; separate portions of 5 cc. each yield no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution (*sulfate*), no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metal*).

Dry about 0.5 Gm. of metycaine hydrochloride, accurately weighed, over sulfuric acid in a desiccator for 48 hours; the loss does not exceed 0.25 per cent. Incinerate about 0.5 Gm., accurately weighed; the residue is not more than 0.2 per cent. Transfer about 0.25 Gm. to a 400 cc. beaker, add 100 cc. of water followed by the addition of 25 cc. of tenth normal silver nitrate solution and 10 cc. of nitric acid; boil with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with nitric acid and water, followed by alcohol and ether, finally dry to

of tenth-normal hydrochloric acid solution followed by the addition of an equal amount of water determine the excess of acid by titration with twentieth normal sodium hydroxide solution using methyl red as an indicator the amount of tenth normal hydrochloric acid solution consumed corresponds to not less than 86.5 per cent nor more than 88 per cent benzoyl γ (2 methyl piperidino) propanol

ELI LILLY AND COMPANY

Solution Metycaine Hydrochloride 1%, 1 cc ampuls
Each cc contains metycaine hydrochloride 10 mg in isotonic solution of sodium chloride

Solution Metycaine Hydrochloride 2% and Epinephrine (1:25,000) 1 cc ampuls Each cc contains metycaine hydrochloride 10 mg epinephrine 0.04 mg and thiourea 0.3% in Ringer's solution

The thiourea which is added to the dosage forms containing epinephrine in order to prevent oxidation complies with the tests and standards given in the chapter on Pharmaceutical Aids

Solution Metycaine Hydrochloride 2%, and Epinephrine (1:50,000) 2.5 cc ampuls Each cc contains metycaine hydrochloride 20 mg epinephrine 0.02 mg, and thiourea 0.15% in Ringer's solution

Solution Metycaine Hydrochloride 10%, 2 cc ampuls
Each 2 cc contains metycaine hydrochloride 0.2 Gm in distilled water To be used for spinal anesthesia

Solution Metycaine Hydrochloride 20%, 5 cc ampuls
Each 5 cc contains metycaine hydrochloride 1 Gm in distilled water To be used for infiltration and regional anesthesia The solution must be diluted before use

Metycaine Hydrochloride Ophthalmic Ointment 4 per Cent Metycaine hydrochloride 4 per cent in a base consisting of liquid petrolatum wool fat and with small amounts of paraffin white petrolatum and ceresin

Metycaine Hydrochloride Ointment 5% Metycaine hydrochloride 5 per cent in a base consisting of white petrolatum with white wax and wool fat

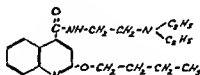
Solution Metycaine Hydrochloride 2% Metycaine hydrochloride 2% in isotonic solution of sodium chloride containing chlorbutanol 0.5% as preservative

Tablets Metycaine Hydrochloride 0.15 Gm and 32 mg

U. S. patent 1,784,903 (Dec. 16, 1930 expires 1947) U. S. trademark 305,894

NUPERCAINE HYDROCHLORIDE — Dibucaine — β diethylaminoethylamide of 2 butoxycinchonic acid hydrochloride 2 butoxy 4 (β diethylaminoethylamido) carboxy quinoline

heating with sodium butylate



Actions and Uses—Nupercaine hydrochloride is a local anesthetic, acting like cocaine when applied to mucous surfaces and like procaine or cocaine when injected, the action being relatively prolonged. Nupercaine hydrochloride is about five times as toxic as cocaine when it is injected intravenously into animals, and its anesthetic activity is correspondingly greater than that of cocaine when it is applied to a mucous surface. It is many times more active than procaine hydrochloride when it is injected subcutaneously. It is reported to have caused necrosis of tissue in one case and a condition resembling gangrene with recovery in another. Death has been reported after the subcutaneous injection of 135 cc of a solution of 1 in 1,000. Weak solutions (1 in 2,000) cause slight temporary vascular dilatation (avoided by the addition of epinephrine hydrochloride), followed by constriction.

Dosage—For infiltration anesthesia solutions of from 1 in 2,000 to 1 in 1,000, with the addition of 0.1 cc of epinephrine hydrochloride solution (1 in 1,000) to 100 cc of the solution. Not more than 100 cc. of 1 in 1,000 solution should be injected. For spinal anesthesia, a total of from 7.5 to 10 mg. in 1 in 200 solution, for sacral anesthesia 25 to 35 cc of 1 in 1,000 solution or a correspondingly smaller volume of 1 in 500 solution. Aqueous solutions of nupercaine hydrochloride should be prepared with distilled water, as the salts present in tap water of many localities may precipitate the free base, butyloxycinchonic acid diethylethylenediamide. Alkali-free glass should be used in the preparation of its solutions. (See caution under the general article, Local Anesthetics.)

Tests and Standards—

Nupercaine hydrochloride occurs as fine white crystalline odorless powder, hygroscopic, very soluble in water about 2 in 1, freely soluble

melts at 90 to 98 C

Transfer about 0.5 Gm. of nupercaine hydrochloride to a suitable Squibb separatory funnel, add 25 cc. of water, followed by the addition of 2 cc. of normal sodium hydroxide solution and extract with three

Dry about 0.5 Gm. of nupercaine hydrochloride accurately weighed over sulfuric acid in a desiccator for forty-eight hours the loss does

methyl red as an indicator the amount of tenth normal hydrochloric acid solution consumed corresponds to not less than 88.5 per cent nor more than 90.5 per cent butyloxycinchoninic acid diethylethylenediamide calculated to the dried substance

CIBA PHARMACEUTICAL PRODUCTS, INC

Nupercaine Hydrochloride (Powder) 1 Gm. and 5 Gm.

Buffered Solution Nupercaine Hydrochloride 1 200
2 cc ampuls

Solution Nupercaine Hydrochloride 1 1,000 5 cc and
25 cc ampuls

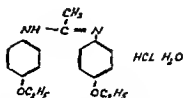
Solution Nupercaine Hydrochloride 1 1,500 in 0.5%
Solution of Sodium Chloride 20 cc ampuls

Solution Nupercaine Hydrochloride 1 1,000, with Epi-
nephrine, 1 100,000 2 cc and 5 cc ampuls

Solution Nupercaine Hydrochloride 2%

Tablets Nupercaine Hydrochloride 50 mg

U. S. patent 1,825,623 U. S. trademark 266,366



For description and standards see the U S Pharmacopeia under Phenacaine Hydrochloride

Actions and Uses—Phenacaine hydrochloride is a local anesthetic like cocaine but having the advantage of a quicker effect. Five minims of a 1 per cent solution when instilled into the eye is usually sufficient to cause anesthesia in from one to ten minutes. This is preceded by temporary smarting.

Dosage—It is applied in a 1 per cent aqueous solution. Phenacaine hydrochloride is incompatible with alkalis and their carbonates and the usual alkaloidal reagents. Glass vessels should be avoided in preparing the solution, porcelain being used instead. The solutions are stable as the drug is itself antiseptic. They are not injured by boiling.

MANHATTAN EYE SALVE COMPANY, INC

Holocaine Ointment 1% Collapsible ophthalmic tubes. Holocaine (phenacaine hydrochloride) 1 per cent, water 1 per cent, wool fat 5 per cent and petrolatum sterile 93 per cent.

Holocaine and Adrenalin Ointment Collapsible ophthalmic tubes. Composed of holocaine (phenacaine hydrochloride) 1 per cent, adrenalin chloride solution 2 per cent, water 1 per cent, wool fat 10 per cent, white petrolatum sterile 86 per cent.

WERNER DRUG & CHEMICAL CO

Phenacaine Hydrochloride (Powder) bulk and 1 Gm, 3.54 Gm, 28.35 Gm, 113.4 Gm and 453.6 Gm packages.

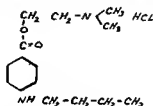
WINTHROP CHEMICAL COMPANY INC

Holocaine Hydrochloride (Powder) bulk. Phenacaine hydrochloride.

Holocaine Hydrochloride Solution 1 per Cent An aqueous solution containing phenacaine hydrochloride 1 per cent for ocular anesthesia by instillation. The product is not to be used for injection.

TETRACAINE HYDROCHLORIDE—U S P—Pon-
tocaine Hydrochloride—When dried over sulfuric acid for
18 hours contains not less than 86.5 per cent and not more
than 88.5 per cent of tetracaine ($C_{18}H_{24}N_2O_2$) U S P

The base of tetracaine hydrochloride belongs to the procaine type. It differs from procaine base in that one of the hydrogens of the paraamino group is replaced by a butyl group and the two ethyl groups of procaine are replaced by two methyl groups in tetracaine base.



For description and standards see the U S Pharmacopeia under Tetracaine Hydrochloride

Actions and Uses—Tetracaine hydrochloride is a local anesthetic with actions similar to those of procaine hydrochloride but it is effective when applied to mucous membranes in lower concentrations. (See caution under the general article Local Anesthetics.) It is used for surface anesthesia in the eye, nose and throat and in spinal anesthesia in which the anesthesia is prolonged.

A special dosage form of tetracaine hydrochloride may also be used to induce continuous caudal analgesia for use in obstetric cases *provided the procedure is carried out with great care and caution and is undertaken only by skilled specialists. It is not a procedure for untrained hands.* Two techniques have been used: one involves the use of a special malleable needle; the other a ureteral catheter. When the special needle is used, great care must be taken to see that that portion of the needle which lies outside the skin is protected so that movement of the patient will not force the needle up into the caudal canal or against bone or into a vein. Further, the needle must be protected against breakage. The patient should not be allowed to remain in a sitting position but be instructed to lie on her side. If the needle breaks within the canal, it must be removed within a few hours. Of course such things as penetration of blood vessel and dura should be watched for constantly when the needle is being inserted.

If a ureteral catheter is to be employed, entry into the caudal canal should be made with a needle no larger than 15 gauge. If it is necessary to use a needle as large as 13 gauge and the caudal canal is not entered on the first attempt, the method should be discarded; otherwise infection is almost certain to occur. Infection is one of the great dangers encountered in

continuous caudal analgesia and extreme care must be exercised to prevent this condition. There should be at hand emergency measures to control untoward reactions. Soluble barbiturate is useful to control convulsions should they occur. Oxygen should be immediately accessible.

Continuous caudal analgesia is contraindicated in the presence of placenta praevia, inertia uteri, uncontrollable hysteria and disproportion of child and pelvis. It is not suitable for difficult forceps rotation or version, as in such cases complete relaxation of the uterus is imperative. History of sensitivity to this anesthetic is another contraindication.

The Council has recognized the use of this local anesthetic to produce caudal analgesia so that proper warnings may be issued. It is emphasized again that this procedure should be carried out only by experienced hands and then only with great caution. Much work remains to be done before the technique will receive final evaluation.

Dosage—Solution of tetracaine hydrochloride 0.5 per cent is used in the eye; a 2 per cent solution is applied to the nose and throat. The 1 per cent solution is injected for spinal anesthesia for which purpose the dose is from 1 to 2 cc. (containing from 10 to 20 mg. of the salt).

For continuous caudal analgesia the appropriate dosage form

An initial skin wheal is raised with the local anesthetic and the underlying tissues infiltrated so that the needle to be inserted into the sacral canal may be inserted without too much discomfort by the patient. Thirty cc. tetracaine hydrochloride 0.25 per cent solution is injected. Signs of fulness in one or both legs, progressive loss of painful sensations and relief of abdominal uterine cramps will from five to fifteen minutes indicate that the analgesic solution has produced its effects. Supplementary injections depend on the individual patient. Usually from 10 to 20 cc. of tetracaine hydrochloride 0.25 per cent solution injected at intervals of from 40 to 90 minutes are sufficient to keep the patient comfortable during the entire course of labor. In many cases approximately 100 cc. of the 0.25 per cent solution would be sufficient for the management of labor and delivery and repairs.

WINTHROP CHEMICAL COMPANY, INC.

Pontocaine Hydrochloride 'Niphanoid' for Spinal Anesthesia 10 mg., 20 mg. and 250 mg. Ampuls containing tetracaine hydrochloride in finely divided and instantly soluble form. The trade term Niphanoid (from the Greek snow like) is applied to the process whereby dilute solutions of the

rug are subjected to rapid freezing and subsequent evaporation of the solvent under high vacuum the resultant material is claimed to be more readily soluble

Pontocaine Hydrochloride Solution, 1 per Cent 2 cc ampuls Each 2 cc of solution contains tetracaine hydrochloride 20 mg sodium chloride 13.3 mg and acetone bisulfite 4 mg

Pontocaine Hydrochloride Solution, 0.5 per Cent 15 cc. bottles Contains 0.4 per cent chlorobutanol as a preservative

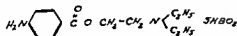
Pontocaine Hydrochloride Solution, 2 per Cent 30 cc and 120 cc bottles The solution contains 0.4 per cent chlorobutanol as a preservative and is tinted with methylene blue to prevent accidental use for injection

Pontocaine Hydrochloride Tablets 0.1 Gm Each tablet contains tetracaine hydrochloride 0.1 Gm boric acid 5 mg acetone sodium bisulfite not more than 0.5 mg To be used only for preparing solutions for surface anesthesia (not for injection) in rhinolaryngology ophthalmology and dentistry

Pontocaine Base Eye Ointment An ointment containing 0.5 per cent of tetracaine base the free base of tetracaine hydrochloride dissolved in white petrolatum

U S patent 1 889 645 (Nov 29 1932 expires 1949) U S trade mark 282 418

PROCAINE BORATE — *p* aminobenzoyl diethylamino ethanol penta *m* borate β diethylaminoethyl *p* amino benzoate penta *m* borate $C_6H_4NH_2COO C_2H_5N(C_2H_5)_2 \cdot 5HBO_2$ — A borate formed by the interaction of *p* aminobenzoyl diethylaminoethanol (procaine base) and boric acid in the same organic solvent Procaine borate contains 51.8 per cent of *p* amino benzoyl diethylaminoethanol



Actions and Uses — Procaine borate closely resembles procaine hydrochloride in its actions and uses The molecule is heavier than that of procaine hydrochloride but the toxicity and the anesthetic activity are closely proportional to the procaine base which they contain When injected subcutaneously procaine borate exerts a prompt and powerful anesthetic action It is relatively nonirritant The testimony concerning its activity when applied to mucous membranes lacks uniformity (See caution under the general article Local Anesthetics)

Dosage — For infiltration anesthesia solutions of 0.5 to 1 per cent for blocking nerves from 1 to 2 per cent for tonsillectomy 0.5 to 1 per cent mucous surfaces 2 to 20 per cent dependent on the location and the depth of anesthesia required Its action is enhanced by the addition of a small amount of epinephrine as in the case of procaine hydrochloride Owing

to the smaller content of the base in procaine borate, the total dose may exceed that of procaine hydrochloride by about 50 per cent

Tests and Standards—

Procaine borate occurs as a fine, white, odorless crystalline powder,

Transfer about 1 Gm of procaine borate to a suitable Squibb separatory funnel add 25 cc of water, followed by the addition of 5 cc of normal sodium hydroxide solution and extract with 3 successive portions of chloroform using 25 cc, 20 cc and 10 cc, respectively, evaporate the combined chloroformic solutions to dryness, dissolve the oily semisolid base in 25 cc of a 2 per cent solution of hydrochloric chloride. Dissolve 0.1 Gm of procaine borate in 2 cc of methyl alcohol, add 5 drops of sulfuric acid and ignite the mixture a green mantle is imparted to the flame. Dissolve 0.5 Gm of procaine borate in 50 cc of water separate portions of 10 cc each yield no opalescence with 1 cc of diluted nitric acid and 1 cc of silver nitrate solution (chloride), no turbidity with 1 cc of diluted hydrochloric acid and 1 cc of barium chloride solution (sulfate), no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals)

combined filtrates to dryness in a tared beaker and dry to constant weight over sulfuric acid in a partially exhausted desiccator, the only residue should not exceed 2 per cent (limit of uncombined *p*-aminobenzoyl diethylaminoethanol)

Dry about 1 Gm of procaine borate, accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty eight hours the loss does not exceed 2 per cent. Transfer about 0.4 Gm of pro-

of warm air, and dry to constant weight over sulfuric acid in a partially exhausted desiccator dissolve the only residue in about 10 cc of previously neutralized alcohol, add 10 cc of tenth normal hydrochloric acid solution, followed by the addition of an equal volume of water, determine the excess of acid by titration with fiftieth normal sodium hydroxide solution, using methyl red as an indicator the amount of tenth normal hydrochloric acid solution consumed corresponds to not less than 50.0 per cent nor more than 52.0 per cent *p*-amino-benzoyl

48.5 per cent *m*-boric acid (H_2BO_3), calculated to the dried substance

PROCAINE HYDROCHLORIDE—Procaine.—U S P.

For description and standards see the U S Pharmacopeia under Procaine Hydrochloride and the National Formulary

under Ampuls of Procaine Hydrochloride Solution of Procaine Hydrochloride and Tablets of Procaine Hydrochloride

Actions and Uses—Procaine hydrochloride is a local anesthetic, less toxic than cocaine and most other cocaine substitutes. When injected subcutaneously it exerts a prompt and powerful anesthetic action, but the effect is not sustained. This may be remedied by the simultaneous injection of epinephrine. Procaine hydrochloride is only slightly irritant.

It is relatively ineffective when applied to intact mucous membranes. (See caution under the general article, Local Anesthetics.)

Dosage—For infiltration anesthesia solutions of 0.25 Gm procaine hydrochloride in 50 or 100 cc isotonic solution of sodium chloride, with 0.3 or 0.6 cc of epinephrine hydrochloride solution (1 in 1000), for instillations and injections solutions of 0.1 Gm procaine hydrochloride in 10 or 5 cc isotonic solution of sodium chloride, with or without 0.6 cc of epinephrine hydrochloride solution (1 in 1000). In ophthalmology, 1 to 5 or even up to 10 per cent solutions and in rhinolaryngology 5 to 20 per cent solutions are recommended with the addition of 0.4 to 0.5 cc of epinephrine hydrochloride solution (1 in 1000) to each 10 cc.

ABBOTT LABORATORIES

Procaine Hydrochloride (Crystals) bulk

Sterile Procaine Hydrochloride Crystals for Spinal Anesthesia 50 mg, 100 mg, 120 mg, 150 mg and 200 mg ampuls

Procaine Hydrochloride Tablets 70 mg, 0.15 Gm and 0.2 Gm. One tablet dissolved in 4 cc, 8 cc or 10 cc of distilled water respectively, makes a 2 per cent solution of procaine hydrochloride.

Procaine Hydrochloride Hypodermic Tablets 20 mg and 50 mg

Procaine Hydrochloride 20 mg, Epinephrine 0.016 mg Hypodermic Tablets: Each contains procaine hydrochloride 20 mg, epinephrine 0.016 mg, sodium bisulfite 16 mg and sodium chloride sufficient so that when the tablet is dissolved in 1 cc of water, the resulting solution is approximately isotonic and contains 2 per cent procaine hydrochloride and 1/60,000 epinephrine hydrochloride.

Procaine Hydrochloride 50 mg, Epinephrine 0.05 mg Hypodermic Tablets: Each contains procaine hydrochloride 50 mg, epinephrine 0.05 mg, sodium bisulfite 16 mg and sodium chloride sufficient so that when the tablet is dissolved in 1 cc of water, the resulting solution is approximately isotonic and contains 2 per cent procaine hydrochloride and 1/60,000 epinephrine hydrochloride.

Procaine Hydrochloride 20 mg, Epinephrine 0.04 mg Hypodermic Tablets Each contains procaine hydrochloride 20 mg epinephrine 0.04 mg and sodium chloride sufficient so that when the tablet is dissolved in 1 cc. of water, the resulting solution is approximately isotonic and contains 2 per cent procaine hydrochloride and 1:25,000 epinephrine hydrochloride

Procaine Hydrochloride Solution 1%, 100 cc bottle Each cc. contains procaine hydrochloride 10 mg sodium chloride 6 mg sodium bisulfite 1 mg and distilled water

Procaine Hydrochloride Solution 1%, 15 cc ampuls Each ampul contains procaine hydrochloride 15 mg in chemically pure water with sodium chloride sufficient to make an isotonic solution

Procaine Hydrochloride Solution 2%, 1 cc and 5 cc ampuls Each cc contains procaine hydrochloride 20 mg and sodium chloride 5 mg in distilled water to make an isotonic solution

Procaine Hydrochloride Solution 2%, 100 cc vials Each cc. contains procaine hydrochloride 20 mg sodium chloride 44 mg sodium bisulfite 1 mg in sterile distilled water

Procaine Hydrochloride Solution 10%, for Spinal Anesthesia 2 cc ampuls Each cc contains procaine hydrochloride 0.1 Gm in distilled water

Procaine Hydrochloride 1% — Epinephrine 1:50,000 Solution 2 cc ampuls Each cc contains procaine hydrochloride 10 mg epinephrine hydrochloride 0.02 mg and sodium bisulfite 1 mg in distilled water to make an isotonic solution

Procaine Hydrochloride 2% — Epinephrine 1:25,000 Solution 1 cc ampuls Each cc contains procaine hydrochloride 20 mg epinephrine hydrochloride 0.04 mg sodium bisulfite 1 mg and potassium sulfate 9 mg in distilled water to make an isotonic solution

Procaine Hydrochloride 2% — Epinephrine 1:25,000 Solution 100 cc bottles Each cc contains procaine hydrochloride 20 mg epinephrine hydrochloride 0.04 mg sodium bisulfite 1 mg and potassium sulfate 9 mg in distilled water to make an isotonic solution

Procaine Hydrochloride Solution 2%, 2 cc ampuls Each cubic centimeter contains 20 mg in isotonic solution of sodium chloride

Ephedrine Hydrochloride 2½%, and Procaine Hydrochloride 1% Solution (See under Ephedrine Hydrochloride)

Ephedrine Hydrochloride 5%, and Procaine Hydrochloride 1% Solution (See under Ephedrine Hydrochloride)

GEORGE A. BREON & COMPANY

Procaine Hydrochloride Solution 2%, 2 cc ampuls
Each cubic centimeter contains 20 mg in isotonic solution of sodium chloride

BRISTOL LABORATORIES, INC

Solution Procaine Hydrochloride 2%, 1 cc ampuls
Each cc contains 20 mg procaine hydrochloride chlorobutanol 5 mg in isotonic solution of sodium chloride

Solution Procaine Hydrochloride 1% and Epinephrine
3 cc ampuls Each cc contains 10 mg epinephrine hydrochloride 0.04 mg chlorobutanol 5 mg and sodium bisulfite 1 mg in isotonic solution of sodium chloride

THE DRUG PRODUCTS CO., INC

Solution Procaine Hydrochloride 2%, 2 cc hypodermics
Each cc contains 20 mg of procaine hydrochloride in isotonic solution of sodium chloride

ENDO PRODUCTS, INC

Solution Procaine Hydrochloride 2%, W/V 2 cc ampuls
Each cubic centimeter contains 20 mg of procaine hydrochloride 5 mg of chlorobutanol and 1 mg of sodium bisulfite in distilled water

Solution Procaine " " " " " " " "
1:20,000 3 cc ampuls
of procaine hydrochloride
chlorobutanol and 1 mg

Solution Procaine Hydrochloride 2%, W/V 30 cc and 100 cc vials
Each cubic centimeter contains 20 mg procaine hydrochloride 5 mg of chlorobutanol and 1 mg of sodium bisulfite in distilled water

Solution Procaine Hydrochloride 2%, with Epinephrine
1:25,000 30 cc and 100 cc vials Each cubic centimeter contains 20 mg of procaine hydrochloride 0.04 mg of epinephrine 5 mg of chlorobutanol and 1 mg of sodium bisulfite in distilled water

LAKEVIEW LABORATORIES, INC

Procaine Hydrochloride 2%, 30 cc and 100 cc vials
Each cubic centimeter contains procaine hydrochloride 20 mg sodium bisulfite 1 mg and chlorobutanol 5 mg in isotonic sodium chloride solution

MERCK & CO., INC

Procaine Hydrochloride (Crystals) bulk

THE WM S MERRILL CO., IOPSEN LABORATORY DIVISION

Sterile Solution Procaine Hydrochloride 1%, 1 cc. and 10 cc ampuls Each cc contains procaine hydrochloride 10 mg in isotonic solution of sodium chloride

Solution Procaine Hydrochloride 2%, 1 cc and 10 cc ampuls Each cc contains procaine hydrochloride 20 mg in isotonic solution of sodium chloride 40 cc and 160 cc bottles

E S MILLER LABORATORIES, INC

Sterile Solution Procaine Hydrochloride 1%, W/V 30 cc, 50 cc and 100 cc vials and 2 cc. and 5 cc ampuls Vials preserved with 0.5 per cent chlorobutanol

Sterile Solution Procaine Hydrochloride 2%, W/V 30 cc 50 cc and 100 cc vials and 2 cc. and 5 cc ampuls Vials preserved with 0.5 per cent chlorobutanol

F R SQUIBB & SONS

Sterile Procaine Hydrochloride Crystals for Spinal Anesthesia 50 mg 100 mg 120 mg 150 mg 200 mg and 500 mg ampuls Bottles of 30 Gm and 100 Gm

THE UPJOHN COMPANY

Hypodermic Tablets Procaine Hydrochloride 50 mg Each contains procaine hydrochloride 50 mg with sodium chloride as a base One tablet dissolved in 1 cc of distilled water makes a 5 per cent solution of procaine hydrochloride

Sterile Solution Procaine Hydrochloride 2%, 30 cc rubber capped vials and 100 cc bottles Each cubic centimeter contains chlorobutanol 50 mg procaine hydrochloride 20 mg sodium bisulfite 10 mg sodium chloride 8.4 mg

Hypodermic Tablets Procaine Hydrochloride 20 mg with Epinephrine 0.025 mg Each contains procaine hydrochloride 20 mg epinephrine 0.025 mg sodium chloride 13 mg benzoic acid 0.3 mg sodium bisulfite 0.125 mg and boric acid 2.27 mg One tablet dissolved in 1 cc of distilled water makes a 2 per cent solution of procaine hydrochloride

Solution Procaine Hydrochloride 2%, with Epinephrine 3 cc ampuls Each cc contains procaine hydrochloride 20 mg epinephrine 0.05 mg sodium bisulfite 2.6 mg benzoic acid 0.3 mg sodium chloride 8.3 mg and normal hydrochloric acid 0.0016 cc in distilled water saturated with carbon dioxide

Solution Procaine Hydrochloride 2%, with Epinephrine 30 cc vials Each cc contains procaine hydrochloride 20 mg epinephrine 0.05 mg sodium bisulfite 2.6 mg benzoic acid

0.3 mg sodium chloride 8.3 mg normal hydrochloric acid 0.0016 cc and chlorobutanol not to exceed 5 mg in distilled water saturated with carbon dioxide

U S STANDARD PRODUCTS CO

Solution Procaine Hydrochloride 2%, with Epinephrine
1 25 000 1 cc ampuls Each cc contains procaine hydrochloride 20 mg epinephrine hydrochloride 0.04 mg and sodium bisulfite 0.45 mg in distilled water

WINTHROP CHEMICAL COMPANY, INC

Novocain (Crystals) bulk Procaine hydrochloride

Sterile Crystals Novocain for Spinal Anesthesia 50 mg 100 mg 120 mg 150 mg 200 mg 300 mg and 500 mg ampuls

Tablets Novocain 65 mg

Novocain Hypodermic Tablets 50 mg

Novocain Hypodermic Tablets 0.2 Gm Each contains procaine hydrochloride 0.2 Gm and sodium chloride 60 mg

Novocain 20 mg and 1 Suprarenin Synthetic Bitartrate 0.02 mg Hypodermic Tablets

Novocain 20 mg and 1 Suprarenin Synthetic Bitartrate 0.05 mg Hypodermic Tablets

Novocain 50 mg with 1 Suprarenin Synthetic Bitartrate 0.083 mg Hypodermic Tablets

Novocain 60 mg and 1 Suprarenin Synthetic Bitartrate 0.06 mg Hypodermic Tablets

Novocain 80 mg and 1 Suprarenin Synthetic Bitartrate 0.06 mg Hypodermic Tablets

Novocain 0.1 Gm and 1 Suprarenin Synthetic Bitartrate 0.25 mg Hypodermic Tablets

Novocain 0.125 Gm and 1 Suprarenin Synthetic Bitartrate 0.13 mg Hypodermic Tablets

Novocain Suprarenin Solution 1 per Cent 30 cc bottles Each cc contains procaine hydrochloride 10 mg epinephrine bitartrate 0.01 mg sodium chloride 4 mg potassium sulfate 4 mg

Novocain Solution 1 per Cent 2 cc and 6 cc ampuls Each cc contains procaine hydrochloride 10 mg and sodium chloride 6 mg in distilled water

Novocain Solution 2 per Cent 3 cc ampuls Each cc contains procaine hydrochloride 20 mg and sodium chloride 4 mg in distilled water

Novocain Solution 10 per Cent for Spinal Anesthesia 2 cc ampuls Each cc contains procaine hydrochloride 0.1 Gm in distilled water

Sterile Solution Novocain 20 per Cent 15 cc and 5 cc ampuls Each cc contains procaine hydrochloride 0.2 Gm in distilled water This solution must be diluted before use

Novocain Solution 1 per Cent with 1 Suprarenin Synthetic Bitartrate 1 50 000 2 cc and 6 cc ampuls Each cc contains procaine hydrochloride 10 mg synthetic epinephrine bitartrate 0.02 mg sodium chloride 45 mg and potassium sulfate 4 mg in distilled water

Novocain Solution 2 per Cent with 1 Suprarenin Synthetic Bitartrate 1 50 000 1 cc ampuls Each cc contains procaine hydrochloride 20 mg and synthetic epinephrine bitartrate 0.02 mg in distilled water

Novocain Solution 2 per Cent with 1-Suprarenin Synthetic Bitartrate 1 50 000 3 cc ampuls Each cc contains procaine hydrochloride 20 mg synthetic epinephrine bitartrate 0.02 mg sodium chloride 45 mg and potassium sulfate 4 mg in distilled water

Novocain Solution 2 per Cent with 1 Suprarenin Synthetic Bitartrate 1 20 000 1 cc and 6 cc ampuls Each cc contains procaine hydrochloride 20 mg and synthetic epinephrine bitartrate 0.05 mg in distilled water

Novocain Solution 2 per Cent with 1-Suprarenin Synthetic Bitartrate 1 20 000 3 cc ampuls Each cc contains procaine hydrochloride 20 mg synthetic epinephrine bitartrate 0.05 mg sodium chloride 45 mg and potassium sulfate 4 mg in distilled water

Sterile Solution Novocain 20 per Cent with 1 Suprarenin Synthetic Bitartrate 1 9 000 15 cc and 5 cc ampuls Each cc contains procaine hydrochloride 0.2 Gm and synthetic epinephrine bitartrate 0.11 mg in distilled water This solution must be diluted before use

Ephedrine-Novocain Solution 1 cc and 2 cc ampuls Each ampul contains procaine hydrochloride 1 per cent and ephedrine hydrochloride 5 per cent in sterile distilled water

U S patent 812 554 (Feb 13 1906 exp red) U S trademark 53 072

PRODUCED BY THE NATIONAL BUREAU OF STANDARDS

Actions and Uses—The same as those of procaine hydrochloride It may be prescribed in combination with silver salts

with which it forms no precipitate (See caution under the general article Local Anesthetics)

Dosage—Like that of procaine hydrochloride

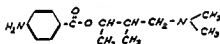
Tests and Standards—

Procaine nitrate occurs in small colorless and odorless crystals soluble in water and alcohol. The aqueous solution is neutral in reaction. The melting point is from 100 to 102 C.

If 0.1 Gm. of procaine nitrate is dissolved in 1 cc. of concentrated

TUTOCAINE HYDROCHLORIDE—Butamin—
p-aminobenzoyldimethylaminomethyl butanol hydrochloride—

mixture =



Acti
 cutane
 When
 compl.

tively low concentrations

It is reported that complete anesthesia of the cornea occurs

used by injection the effects are very prompt

In wheel tests on human beings a 1 per cent tutocaine hydrochloride solution produced an anesthesia that lasted for from fifteen to twenty minutes, a 0.125 per cent solution containing epinephrine gave an anesthesia that lasted for about two hours. In experiments made for the council, tutocaine hydrochloride in 3 per cent solution was found to be about four times as toxic as procaine hydrochloride by rapid intravenous injection into the cat. A fatality has been reported following the injection of 8 cc. of a 2 per cent solution into the urethra (See caution under the general article Local Anesthetics). On the other hand experiments and clinical trials have been reported in support of the claim that tutocaine hydrochloride is relatively safe for use in surface anesthesia and by hypodermic injection.

Dosage—For application to the eye, nose and throat 2 to 5 per cent solutions of tutocaine hydrochloride are used, for applications to the urethra, 0.5 to 1 per cent solutions, increased to 2 per cent in very painful procedures, for infiltration anesthesia, 0.2 per cent solutions are generally used.

Tutocaine hydrochloride solutions may be sterilized by boiling for a short time.

Tests and Standards—

Tutocaine hydrochloride occurs as a light ivory colored crystalline powder. It is practically odorless, when applied on the tongue, it produces a faintly bitter taste followed by a sense of numbness, it is stable in air. It is easily soluble in water (about 1 in 4), and difficultly soluble in alcohol (1 in 50). An aqueous solution (1 in 10) is neutral to litmus paper. It is optically inactive. It melts at from 212 to 215 C. From aqueous solutions, alkali hydroxides and carbonates precipitate the free base tutocaine as a light yellowish oil which solidifies on standing and melts at not less than 81 C.

precipitate with 1 cc of nitric acid and 1 cc of silver nitrate solution. Dissolve 0.1 Gm in 5 cc of water, add 2 drops diluted hydrochloric acid and 1 cc of barium chloride solution. no precipitate forms (distinction from butyrocaine). add 3 drops of a potassium permanganate solution. immediately (distinctly) decolorized by sulfuric acid. 0.1 Gm in 10 cc of water. no coloration or precipitate.

Dry about 1 Gm of tutocaine hydrochloride accurately weighed to constant weight at 100 C. the loss does not exceed 1 per cent. Incinerate about 0.5 Gm accurately weighed. the residue does not exceed 0.2 per cent.

Dissolve about 1 Gm of tutocaine hydrochloride, previously dried and accurately weighed, in 15 cc of water. the solution is normal saline. the concentration is not more than 101 per cent.

WINTHROP CHEMICAL COMPANY, INC

Tablets Tutocaine Hydrochloride, 30 mg with Suprenin Bitartrate 0.15 mg

Tablets Tutocaine Hydrochloride, 30 mg with Suprenin Bitartrate 0.06 mg.

Tablets Tutocaine Hydrochloride: 50 mg and 100 mg

U S patent 1,474,567 (Nov 20 1923, expired) U S trademark 180 610

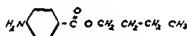
Slightly Soluble Local Anesthetics

The slight solubility of these anesthetics renders them unsuitable for injection but the slow absorption renders them safer especially for ulcers wounds and mucous surfaces. The anesthesia which they induce is usually not so complete as that induced by the soluble local anesthetics but it is more lasting. As a group they are practically nonirritant and nontoxic. Ethyl aminobenzoate (benzocaine anesthetic) and orthoform are about equally effective through intact mucous membranes. butyl aminobenzoate (butesin) is claimed to be more effective than ethyl aminobenzoate.

They are used for painful wounds ulcers etc., of the skin and accessible mucous membranes, for instance after dental operations.

Many if not all local anesthetics occasionally give rise to dermatitis. When this is severe the use of the anesthetic should be discontinued.

BUTYL AMINO BENZOATE—Normal Butyl Amino benzoate—U S P—Butesin



For description and standards see the U S Pharmacopeia under Butyl Aminobenzoate.

Actions and Uses—See preceding article Slightly Soluble Local Anesthetics. The actions and uses of butyl aminobenzoate are similar to those of ethyl aminobenzoate U S P but it is claimed to be more effective.

Dosage—Butyl aminobenzoate is used as a dusting powder either with or without a diluent. It may be used in the form of troches ointment or suppositories or dissolved in a fatty oil. Its oil solutions may be sterilized by heat.

ABBOTT LABORATORIES

Butesin (Powder) bulk

U S patent 1 440 657 (Jan 2 1923 exp. 1931) U S trademark 175 095

BUTESIN PICRATE—Dinormalbutyl *p* aminobenzoate trinitrophenol ($\text{C}_6\text{H}_4\text{NH}_2\text{COO C}_4\text{H}_9$), $\text{C}_6\text{H}_3(\text{NO}_2)_3\text{OH}$ —A compound consisting of one molecule of trinitrophenol (picric acid) and two molecules of the normal butyl ester of 4 amino benzoic acid.

Actions and Uses—An aqueous solution of 1 in 2000 produces immediate and complete anesthesia of the eye which lasts

from ten to twenty minutes. Butesin picrate is used in the treatment of burns, ulcers and other denuded painful lesions of the skin.

Instances of butesin picrate dermatitis have occurred which are probably due to idiosyncrasy. A development of a rash following the use of the drug is an indication for its discontinuance.

Dosage—For use a 1 per cent butesin picrate ointment is proposed.

Tests and Standards—

The aqueous solution of butesin picrate is greenish yellow, the color is intensified by the addition of alkali and is decreased by acid. A saturated, aqueous solution of butesin picrate is not affected by the addition of mercuric potassium iodide solution or of silver nitrate solution or of hydrogen sulfide solution. A few drops of sodium nitrite solution added to the acidulated solution of butesin picrate followed by a few drops of a slightly alkaline solution of betanaphthol produces a salmon colored precipitate which quickly darkens. A purplish red color is produced if a 1 per cent potassium cyanide solution be added to an aqueous solution of butesin picrate.

The aqueous solution of butesin picrate is greenish yellow, the color is intensified by the addition of alkali and is decreased by acid. A saturated, aqueous solution of butesin picrate is not affected by the addition of mercuric potassium iodide solution or of silver nitrate solution or of hydrogen sulfide solution. A few drops of sodium nitrite solution added to the acidulated solution of butesin picrate followed by a few drops of a slightly alkaline solution of betanaphthol produces a salmon colored precipitate which quickly darkens. A purplish red color is produced if a 1 per cent potassium cyanide solution be added to an aqueous solution of butesin picrate.

Inclinerate 0.5 Gm of butesin picrate accurately weighed, the ash does not exceed 0.1 per cent.

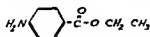
ABBOTT LABORATORIES

Butesin Picrate Ointment with Metaphen Butesin picrate 1 per cent and metaphen 1:5000, incorporated in an ointment base composed of white wax, paraffin, petrolatum, sodium borate and water, 99 per cent.

Ophthalmic Ointment Butesin Picrate 1% and Butesin 1% Butesin picrate 1 per cent, butesin, 1 per cent and soft petrolatum 98 per cent.

U. S. patent 1,596,259 (Aug. 17, 1926 expired) U. S. trademark 175,095.

ETHYL AMINO BENZOATE—Benzocaine U. S. P.—Anesthetic.



For description and standards see the U. S. Pharmacopoeia under Ethyl Aminobenzoate.

Actions and Uses—See preceding article. Slightly Soluble. Local Anesthetics.

Dosage—Used as a dusting powder, either with or without a diluent. It may be applied in ointment or in the form of suppositories.

ABBOTT LABORATORIES

Anesthesin (*Powder*): bulk

U S trademark 55,744

GEORGE A. BREON & Co, INC.

Benzocaine in Oil: Bottles of 15 cc and 480 cc Contains benzocaine 25 per cent W/V and chlorobutanol 05 per cent W/V in cottonseed oil

MERCK & Co, INC.

Benzocaine (*Powder*): bulk

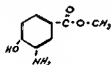
WINTHROP CHEMICAL COMPANY, INC.

Anaesthesin Jelly: 45 cc collapsible tube

Anaesthesin (*Powder*): bulk

U S trademark 55,744

ORTHOFORM.—Orthoform-New — Methyl-*m* amino-*p*-hydroxybenzoate— $C_6H_4NH_2OHCOO(CH_3)$ —The *m*-amino *p*-hydroxybenzoic acid ester of methyl alcohol



Actions and Uses—Orthoform is a local anesthetic, but penetrates the tissues very slowly on account of its insolubility. It has no action on the unbroken skin. It is practically non-toxic in the usual doses.

It has been applied locally as an analgesic to wounds of every description. It has been used in dentistry and in nasal catarrh, hay fever, etc.

Dosage—The Council does not approve of the internal use of this drug. It is used as a dusting powder or mixed with milk sugar for insufflation, dissolved in ether and mixed with oil for penciling, or as an ointment with wool fat, etc.

Tests and Standards—

Orthoform occurs as a fine, white, crystalline powder, neutral in reaction melting at from 141 to 143 C., odorless and tasteless. It is almost insoluble in water, freely soluble in alcohol and soluble in ether. It is decomposed, by boiling with water or by warming with alkalis or their carbonates, into methyl alcohol and *p*-hydroxy *m*-aminobenzoic acid or its alkali salt. When crystallized from chloroform it sometimes assumes the form of white crystals melting at from 110 to 111 C. and returning on melting to the ordinary form.

The filtrate obtained after shaking a small quantity of the orthoform with water produces a transient color with ferric chloride and should not give a reaction with silver nitrate. A solution of 0.1 Gm. of ortho-

form dissolved in 2 cc of water by the aid of hydrochloric acid is colored yellowish red on the addition of sodium nitrite and then deposits a yellow precipitate, deepening to red on exposure to the air

WINTHROP CHEMICAL COMPANY, INC

Orthoform (Powder)— 5 Gm vials, and 311 Gm and 1244 Gm bottles

U S patents 610,348 (Sept 6 1898, expired), and 625 158 (May 16 1899, expired)

General Anesthetics

CYCLOPROPANE — Cyclopropanum — Trimethylene —
 "Contains not less than 99 per cent by volume of C_3H_6 ."—
 U S P

For description and standards see the U S Pharmacopœia under Cyclopropane

Caution—*Cyclopropane is inflammable and its mixture with oxygen or air may explode when brought in contact with a flame or other causes of ignition*

Actions and Uses—Cyclopropane differs from other gaseous anesthetic agents in that the anesthetic oxygen ratio is reversed—15 per cent of cyclopropane to 85 per cent of oxygen up to the rarely and briefly used 40 per cent of cyclopropane and 60 per cent oxygen. The high anesthetic potency of cyclopropane as compared with other hydrocarbons makes its use advantageous from the standpoint that abundant concentrations of oxygen may be used. There is evidence to indicate that the rate of diffusion of cyclopropane is about twice that of ethylene. Cyclopropane is eliminated less rapidly than ethylene but much faster than ether. Induction and recovery with cyclopropane are therefore slower than with ethylene but more rapid than with ether.

There is some evidence to indicate that cyclopropane affects the autonomic tissue of the heart more than ether or chloroform. In high concentrations it heightens the irritability of this tissue and predisposes to the occurrence of cardiac arrhythmias. This effect has been shown to be enhanced with the simultaneous use of epinephrine. For these reasons the pulse must be carefully observed and the use of sympathomimetic drugs avoided during cyclopropane anesthesia. Cyclopropane does not stimulate respiration as do many other general anesthetic agents and for this reason preoperative sedation with respiratory depressants must be used with caution. The signs of Guedel for other anesthetic agents do not apply to cyclopropane, so that familiarity with the signs of the stages of anesthesia for cyclopropane is absolutely essential in the administration of this agent.

The explosibility of cyclopropane oxygen mixtures is not greater than that of other anesthetic oxygen mixtures with the exception of nitrous oxide but, since the latter gas also sup

ports combustion its use with cyclopropane should not be regarded as a safeguard against this hazard. Careful operating room technique to avoid conditions conducive to the production of electrostatic sparks and the presence of open flames and the cautery should be observed with the same precautions as those for other anesthetics.

The advantages of cyclopropane consist in its effectiveness in concentrations providing an adequate supply of oxygen, decreased pulmonary irritation (except in asthmatics), less excitement during induction and low toxicity. Its disadvantages include lack of respiratory stimulation, difficulty in detection of the planes of anesthesia by those unfamiliar in its administration, and tendency to produce cardiac arrhythmias and postanesthetic headache.

Dosage—Cyclopropane is usually furnished in compressed form in metal containers. In use the gas is passed into an inhalation apparatus of the closed circuit type and is then administered by inhalation from a re-breathing bag, always with the admixture of oxygen. The concentration employed varies from 15 to 40 per cent and with the individual patient but should probably not exceed 30 per cent. The remainder of the mixture should consist of a minimum of 20 per cent oxygen, but this should be supplied in quantities adequate for physiologic needs. When other anesthetics are used in combination or when premedication has been employed less cyclopropane is required.

OHIO CHEMICAL & MFG COMPANY

Cyclopropane Cylinders

1 R SQUINN & SONS

Cyclopropane 132 liter 380 liter and 768 liter cylinders

ETHYL CHLORIDE—U S P

For description and standards see the U S Pharmacopeia under Ethyl Chloride for actions and uses see Useful Drugs under Ethyl Chloride

Caution—As the vapor is very inflammable Ethyl Chloride must not be used near flame

MERCK & CO INC

Kelene (Liquid) Ethyl chloride 30 Gm 60 Gm and 100 Gm tubes with automatic closures

U S trademark 63705

ETHYLENE—Contains not less than 90 per cent by volume of CH_4 —U S P

For description and standards see the U S Pharmacopeia under Ethylene

Caution—Ethylene is inflammable and a mixture of it with oxygen or air will explode when brought in contact with a flame or other causes of ignition

Actions and Uses—Animal experiments by W E Brown (*Canad M A J*, March 1923, p 210) and Luckhardt and Carter (*J A M A* 80 765 [March 17] 1923) indicated that ethylene has a direct action on the nervous system when certain high concentrations of ethylene and corresponding low concentrations of oxygen are used, that the motor reflexes are abolished with these concentrations and that the phenomena produced by the undiluted gas are partly asphyxial, which effect can be removed by addition of oxygen to the ethylene itself

Trials on human subjects have confirmed the anesthetic and analgesic value of ethylene as demonstrated on animals First plane surgical anesthesia is stated to be produced easily and analgesia comes on readily and apparently long before surgical anesthesia is established Given with oxygen, it has been found more powerful than nitrogen monoxide (nitrous oxide) and in most instances as effective as ether unlike ether it causes minimal respiratory irritation and does not promote mucus secretion

Extensive use of ethylene in a wide variety of conditions failed to show it to be more explosive than ether oxygen or ether-nitrous oxide oxygen under comparable precautions

Under average conditions of ventilation ethylene, because of its rapid diffusibility, exists in explosive concentration (32 per cent) no further than two feet from the mask Adequate ventilation of this area should eliminate largely the danger of explosion No electrical devices should be employed when ethylene is used The ordinary operating room technique guarding against the presence of open flames, cautery and sparks should be observed

The advantages of ethylene consist in the production of an equally rapid but more pleasant induction, satisfactory relaxation without cyanosis or sweating, rapid recovery and decreased or absent post operative nausea It is useful in older children and in the presence of cardiac lung or kidney disease, thyrotoxicosis and diabetes

Dosage—Ethylene is supplied in compressed state in metal containers For use the gas is passed into an inhalation apparatus and is then inhaled with admixture of oxygen The concentration employed for surgical anesthesia is never in excess of 90 per cent ethylene with 10 per cent oxygen, though after a prolonged period of anesthesia, a deep anesthetic state may be maintained on 80 per cent or less ethylene If the patient has been premedicated (morphine, barbitol) less ethylene and more oxygen can be given Mixtures containing over 50 per cent oxygen should never be employed because of the explosion hazard

THE LIQUID CARBONIC CORPORATION

Ethylene cylinders

OHIO CHEMICAL & MFG COMPANY

Medical Ethylene Gas cylinders

PURITAN COMPRESSED GAS CORPORATION

Ethylene cylinders

TRICHLOROETHYLENE—Trichloroæthylenum—Trichlorethylene—Contains not less than 99 per cent and not more than 99.5 per cent of C_2HCl_3 . U S P

For description and standards see the U S Pharmacopeia under Trichloroethylene

Actions and Uses—The actions of trichloroethylene have not been extensively investigated. It was introduced into therapeutics as a result of observations of prolonged anesthesia of the fifth nerve following trichloroethylene exposure in industry because it was considered to have a selective action on the sensory endings of the trigeminal nerve. However evidence is now accumulating which indicates that it is a general anesthetic rather than a specific nerve anesthetic. It must be remembered that the distribution of the fifth nerve is much greater than that of other nerves supplying the face and that trigeminal neuralgia (tic douloureux) while not a common condition is one of the commonest of the facial neuralgias. It is therefore only natural that the usefulness of this agent in that particular condition should have received such prominence and that the interpretation of the results obtained seemed to indicate a special affinity which did not exist. Regardless of the fact that no special affinity exists trichloroethylene is a useful measure in the treatment of tic douloureux as well as in many other painful conditions of the face.

Trichloroethylene has been proposed for use in the prevention and treatment of attacks of angina pectoris. It is believed that trichloroethylene is worthy of trial for this purpose in the clinic provided patients are under continued medical supervision. Trichloroethylene is a general anesthetic and its use for this purpose is subject to all the dangers and disadvantages of anesthetics. It should never be prescribed in bulk or taken in large doses from 1 to 3 cc a day, in divided doses being ample. The dosage should always be taken with the patient in a reclining position and the material should not be substituted for amyl nitrite or nitroglycerine in the treatment of the acute anginal attack. Each patient should be warned of the possibility of addiction. Excessive dosage of trichloroethylene may mask a severe attack of coronary pain and lead to its being ignored where it should receive immediate medical attention together

with bed rest. It should be used cautiously in the prevention of attacks because it may mask pain indicating exertion beyond the capacity of the heart.

Dosage—One cc by inhalation, to be repeated after a few minutes if necessary, but it appears probable that not more than 4 cc should be inhaled within twenty four hours when it is used for any considerable period of time.

LUDFORD LABORATORIES, INC

Trichlorethylene—1 cc sealed fragile glass tubes. This product contains not more than 0.2 mg of ammonium carbonate per cubic centimeter, to prevent the thermal decomposition of the trichlorethylene vapor which occurs during the sealing process.

VINETHENE—Vinethenum—Vinyl Ether for Anesthesia— $\text{CH}_2=\text{CH}-\text{O}-\text{CH}_2-\text{CH}_3$, with the addition of 3.5 per cent absolute alcohol and 0.01 per cent of phenyl α naphthylamine.

Caution—*Vinethene is inflammable and deteriorates on exposure to air and light. It should not be used for anesthesia if the original container has been opened longer than twenty four hours.*

Actions and Uses—Vinethene is an inhalation anesthetic to be used for short anesthetics. It differs from ether, U. S. P. in the rapidity of its action. This property necessitates special caution in its administration. It is easy to pass from the level of surgical anesthesia to dangerous overdosage, therefore the importance of constant, close observation of the patient cannot be overemphasized. Properly watched, this rapid action is of advantage in short anesthetics, as is the prompt recovery which follows administration of the drug. The patient is completely oriented and ambulant within a few minutes. To prevent recovery from occurring before the surgical procedure is completed, Vinethene must be administered continuously during maintenance.

The anesthetist should familiarize himself thoroughly with the properties of vinethene before employing it. Of major importance is the fact that the eye signs usually depended on in anesthesia are entirely unreliable. The most important single signs to follow in determining the extent of the anesthesia are the rate, depth, regularity and smoothness of respiration. If the anesthesia is administered in the proper way there should be no cyanosis and the development of such a condition is an indication for the employment of oxygen followed by the use of other anesthetic agents. Although there is occasionally an increased secretion of mucus during maintenance, even when atropine is administered postoperative complications have not been frequently encountered. Nausea and vomiting occur in about 5 per cent of cases.

Vinethene is intended primarily for use in minor surgical operations of short duration, and in dentistry where gas anesthesia is not available. It is also useful as an induction anesthetic. It has been rather extensively used during labor and during postpartum obstetric procedures. It has however, one major disadvantage when used in this branch of medicine—its rapid action has practically precluded its use for obtaining obstetric analgesia.

Under no circumstances should the anesthetic be pushed, and if proper relaxation and anesthesia are not obtained with low concentrations other agents should be employed. In case of overdosage respiration is likely to be inhibited and anoxemia and cyanosis are likely to develop. Under such circumstances the anesthetic must be discontinued, oxygen administered, and measures taken to stimulate respiration and provide an adequate airway between the lungs and the atmosphere. The explosive and fire hazards of Vinethene are just about equal to those of ether, U S P.

As with most other anesthetic agents age, cardiovascular disease, renal insufficiency or hepatic damage, particularly the latter, must be given due consideration as contraindications. It may be administered by the open drop semiopen drop or closed machine method. It would seem at the present time that the open drop method is preferable for the short anesthetics. In any case an adequate oxygen or air supply is essential and an unobstructed airway is of paramount importance.

Tests and Standards—

Vinethene occurs as a clear colorless liquid with a slight purple fluorescence possessing a characteristic odor. It is miscible with alcohol chloroform or ether. Vinethene boils at 28.31 C.

Agitate 5 cc of vinethene in a small, chilled glass stoppered cylinder with 2 cc of water (previously boiled and cooled) the aqueous layer should not affect blue or red litmus paper.

Concentrate 10 cc of vinethene to about 1 cc, pour on clean odorless filter paper, no foreign odor becomes perceptible as the last portions disappear from the paper and the paper remains odorless.

Add 1 cc of cold vinethene to 0.5 cc of a cold solution of 1 Gm

of 5% aqueous solution of sodium hydroxide. The solution should be colorless and should not exceed 0.002 Gm

To 3 cc of vinethene add 1 cc of an alkaline solution of phloro-

phorin. The solution should be colorless and should not exceed 0.002 Gm

should not exceed 0.002 Gm

MIRCK & Co., Inc

Vinethene® 10 cc vials and 25, 50 and 75 cc bottles

U S patents 2 021,872 (Nov 19 1935, expires 1952) 2 044,800 (June 23 1936 expires 1953) 2 044,801 (June 23 1936 expires 1953) and 2 099,695 (Nov 23 1937 expires 1954) U S trademark 312 453

Basal Anesthetics

See also Paributuric Acid Derivatives

SOLUTION OF TRIBROMOETHANOL—Solution of Tribromoethyl Alcohol—U S P—Avertin with Amylene Hydrate A solution of tribromoethanol in amylene hydrate containing in each 100 cc not less than 99 Gm and not more than 101 Gm of $C_6H_5Br_3O$ U S P

For description and standards see the U S Pharmacopœia under Solution of Tribromoethanol

Actions and Uses—Solution of Tribromoethanol is used for basal anesthesia by rectal administration. It should not be employed in dosage sufficient to cause complete anesthesia. When employed for basal narcosis the amount of inhalation anesthetic necessary to establish and maintain complete anesthesia is diminished. A prolonged period of sleep usually follows termination of inhalation anesthesia, during this after period careful nursing care and continuous vigilance are necessary to maintain an open airway and to prevent the cyanosis and respiratory failure which sometimes follow. Ephedrine carbon dioxide caffeine with sodium benzoate and oxygen therapy are said to be effective antidotes against respiratory and circulatory depression occurring from solution of tribromoethanol.

Contraindications to the use of solution of tribromoethanol (relative or absolute depending on the condition of the patient) include liver or kidney dysfunction severe cardiac disease hypertension hypotension old age shock or dehydration sepsis toxemia severe pulmonary tuberculosis empyema marked hypothyroidism obesity, asthenia cachexia deep tumors of the colon enteritis and acidosis.

Solution of Tribromoethanol is said to be useful in the control of certain convulsive conditions such as tetanus, in the latter condition it is used in repeated doses in conjunction with administration of tetanus antitoxin to control the seizures over a period of several days if necessary. It is useful in breaking a vicious cycle of status asthmaticus.

Caution—Solution of Tribromoethanol should never be employed by those inexperienced in its use except under expert supervision.

Dosage—For each kilogram of body weight rectal 0.06 cc (1 minim) U S P

Solution of tribromoethanol is administered rectally in 2% per cent solution in warm distilled water at a temperature not exceeding 40 C. A small quantity of the solution should be tested with the congo red indicator supplied with the preparation just before administration, the color of the solution should match that of an equal amount of distilled water containing an equal quantity of the congo red indicator. If the colors do not match this indicates the presence of irritant hydrobromic acid and dibromacetaldehyde and the solution should be discarded.

The ordinary maximum dose for local anesthesia is 80 mg. of tribromoethanol (40 mg. of amylene hydrate) per kilogram of body weight. Often less will be sufficient. In young vigorous persons the dose may sometimes be increased to 90 or 100 mg. of tribromoethanol (from 45 to 50 mg. of amylene hydrate). A dose of 30 to 50 mg. per kilogram is usually sufficient for amnesia and is not accompanied by depression of the respiration or circulation. The dose is usually stated in milligrams of the tribromoethanol component only. As the amylene hydrate adds materially to the narcotic effect it should be kept in mind that with each dose of tribromoethanol, half of its dose by weight of amylene hydrate is administered.

The total amount administered should not exceed from 6 to 8 cc. of solution of tribromoethanol for women or from 9 to 10 cc. for men regardless of weight. Dose tables are supplied by the firm.

WINTHROP CHEMICAL COMPANY, INC.

Avertin with Amylene Hydrate (Solution) Each cc. contains tribromoethanol 1 Gm. and amylene hydrate 0.5 Gm.

U. S. Pat. No. 1,377,000 (Dec. 9, 1920) and 1,377,001 (Dec. 9, 1920)
 U. S. Pat. No. 1,377,002 (Dec. 9, 1920) and 1,377,003 (Dec. 9, 1920) U. S. Pat. No. 1,377,004 (Dec. 9, 1920)

CHAPTER IV

ANTI-INFECTIVES

LOCAL ANTI-INFECTIVES

Criteria for evaluation of skin disinfectants (bacterial) which the Council deems advisable include

- 1 Phenol coefficients or other *in vitro* tests in the absence and in the presence of serum, using both vegetative bacterial cells and clostridial spores, with suitable recovery mediums containing, if known, neutralizing substances for the disinfectant being tested
- 2 Data on germicidal efficiency under conditions simulating actual use by the method of Price (Price P B The Bacteriology of Normal Skin A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleaning, *J Infect Dis* 63 301 [Nov-Dec] 1938 Ethyl Alcohol as a Germicide, *Arch Surg* 38, 52b [March] 1939) or, better still by an extension of the method of Price (Bernstein, L H T Standardization of Skin Disinfectants *J Bacteriol* 43:50 [Jan] 1942) The complications due to possible effects of the germicide on the skin itself should be taken into consideration (Cromwell H W and Leffler, Ruth Evaluation of 'Skin Degerming' Agents by a Modification of the Price Method *ibid* p 51)
- 3 Data on germicidal efficiency by an animal method such for example as suggested by Alice H Kempf and W J Nungester (An *In Vivo* Test for the Evaluation of Skin Disinfectants *ibid*, p 49) or R W Sarber (*ibid*, p 50)
- 4 Evidence from animal experiments regarding irritant action on skin and mucosae and regarding systemic toxicity
- 5 Critical clinical evidence supporting claims of harmlessness and efficacy
- 6 Data on the bacteriostatic activity as distinguished from the germicidal activity of the disinfectant

Alcohols

ISOPROPYL ALCOHOL—Propan-2 ol— $\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$ —Obtained by the reduction of acetone or, as a product in the petroleum industry, by the absorption of olefin gases containing propylene in sulfuric acid, and hydrolyzing the resulting sulfuric acid esters

Actions Uses and Dosage—Isopropyl alcohol because it is a solvent for creosote is used in the removal of that substance from the skin as a prophylactic agent against creosote burns. Isopropyl alcohol has been recommended for the disinfection of the skin and of hypodermic syringes and needles. As it is said not to affect the potency of solutions of insulin it has been employed as a disinfecting agent in connection with the administration of this agent. Until further data are available isopropyl alcohol should not be relied on to destroy such spore-bearing organisms as *Clostridium tetani*, *Clostridium welchii* or *Bacillus anthracis*. Recent investigations indicate that isopropyl alcohol compares favorably with ethyl alcohol so far as anti-infective action is concerned. It is not potable and should not be given by mouth.

Tests and Standards—

Isopropyl alcohol is a clear colorless volatile liquid having a characteristic odor and a slightly bitter taste miscible with water in all proportions also miscible with chloroform and ether. It is a soluble neutral solution and may be recovered from aqueous mixtures by salting out with sodium chloride, sodium hydroxide, etc. Specific gravity at 25°C from 0.780 to 0.790. Refractive index at 20°C from 1.3770 to 1.3780. Isopropyl alcohol is volatile at low temperatures and boils at from 71 to 83°C. It does not affect blue or red litmus paper previously moistened with water when diluted with an equal volume of water.

Evaporate 100 cc of isopropyl alcohol in a platinum dish on a water bath and dry at 100°C. The residue does not exceed 0.01 per cent.

Anthracene Derivatives

ANTHRALIN—C₁₄H₁₀O₂—M. W. 226.22. Dihydroxy anthranol—189 anthracetriol—C₁₄H₁₀O₃—M. W. 240.27. Anthralin may be represented by the following structural formula:



Actions and Uses—Anthralin is recommended as a substitute for chrysarobin in the treatment of psoriasis, having the advantage of less liability to production of dermatitis, less tendency to produce conjunctivitis when used about the face and scalp.

and less tendency to discoloration of the skin. The preparation has also been recommended in the treatment of chronic dermatomycosis and for stimulating action in chronic dermatoses.

Dosage—Anthralin is generally employed in concentrations of from 0.1 per cent up to 10 per cent in ointments or creams. It is always well to begin with smaller dosages because of a tendency to produce an irritation of the skin.

Tests and Standards—

Anthralin occurs as an odorless and tasteless, yellow crystalline powder, which is readily soluble in chloroform, soluble in acetone, alcohol, ether and glacial acetic acid. It is soluble in sodium hydroxide solution, the solution possessing greenish fluorescence and becoming a deep orange red. The melting point of anthralin is from 175 to 181 C.

Dissolve about 0.1 Gm of anthralin in 10 cc of alcohol, and 0.1 cc of diluted ferric chloride solution; a greenish brown color results. Add a few crystals of anthralin to 2 cc of sulfuric acid; an orange-yellow color results (*1,8-dihydroxy-anthraquinone gives a scarlet color*).

Dissolve 0.1 Gm of anthralin in 10 cc of warm acetone; the solution is clear, pour the solution into 200 cc of water; a yellow precipitate results. Add 5 cc of sodium hydroxide solution and mix; the precipitate dissolves and the yellow-colored solution rapidly changes to orange and finally to red.

Add about 0.5 Gm of anthralin to a mixture of 3 cc of anhydrous pyridine and 3 cc of acetic anhydride and boil about fifteen minutes; the yellow needles form and recrystallize from 208 to 210 C.

Add 0.5 Gm of anthralin to 10 cc of water, mix and filter; the filtrate is neutral, separate portions of the filtrate yield no turbidity on the addition of silver nitrate solution, barium nitrate solution or ammonium sulfide solution, and no color on the addition of ferric chloride solution.

Ignite 0.5 Gm of anthralin; the ash is negligible.

Transfer 0.1 Gm of anthralin, accurately weighed to a beaker, add 75 cc of acetone and warm to dissolve the solid. While the solution is hot add 10 cc of silver ammonium nitrate solution (dissolve 3 Gm of silver nitrate in 120 cc of water and add 10 cc of 10 per cent ammonium hydroxide solution), mix and allow to stand at room temperature for two hours. Filter through a suitable Gooch crucible (or sintered glass filter). Wash the beaker and precipitate with ether acetone, then about 300 cc of ammoniacal ammonium nitrate solution (dissolve 15 Gm of ammonium nitrate in 300 cc of water and add 10 cc of ammonium hydroxide solution) and finally wash with acetone. Place the filter in the beaker used for the precipitation of silver, add 10 cc of water and 10 cc of nitric acid and heat to near boiling to facilitate solution of the silver. Add enough water to cover the filter and boil gently for twenty minutes. Add 0.5 Gm of chloride free decolorizing charcoal, mix, let stand for ten minutes and filter while hot through paper. Rinse the beaker and crucible with hot water and finally wash the paper and residue with hot water; combine the filtrate and washings. Cool and titrate with tenth normal ammonium thiocyanate, using 1 cc of 1 per cent ferric nitrate solution as indicator. The amount of silver is not less than 1.35 Gm.

ABBOTT LABORATORIES

Anthralin Ointment: 0.1%, 0.25%, 0.5% and 1% Anthralin in petrolatum base

Anthralin Cream: 0.1%, 0.25% and 0.5% Anthralin in a vanishing cream base of potassium stearate potassium oleate and distilled water

Antibiotics

TYROTHRICIN—An extract first isolated by Dubos obtained from *Bacillus brevis*, a gram positive, aerobic, spore forming soil organism. Tyrothricin possesses antibacterial action against several species of gram positive organisms.

Actions and Uses—Tyrothricin consists of at least two substances, gramicidin and tyrocidin, the former agent being by far the more active component. It seems not unlikely that some of the earlier reports which were claimed to be based on the use of gramicidin were actually concerned with the mixture. Included in the organisms that show some degree of susceptibility are species of pneumococci, streptococci and staphylococci. Its action on bacteria appears to consist, at least in part, of inhibiting enzymatic action, retarding growth and causing lysis.

intravenously. It has been reported to be of value in the treatment of superficial indolent ulcers, the predominating organism of which is gram positive, mastoiditis, empyema and some other wound infections. Its field of usefulness is limited and it appears to exert no effect unless it can come in direct contact with the organisms. Thus it may not exert much effect in the presence of deep seated infections. Body fluids such as saliva, urine and serum offer a slight inhibiting action, whereas substances from gram negative organisms are decidedly inhibiting.

It may be used with caution in body cavities as long as there is no evidence of a gram negative stream. But in no instance should it be used in the presence of a gram negative stream. Experimental stage and much work remains to be done before its true status is established and final comparisons can be made with other antibiotics and anti-infective agents in general.

Dosage—Tyrothricin must be applied locally, not intravenously or by mouth. It is administered after diluting with sterile distilled water to form an isotonic solution in a concentration which yields 400 micrograms of the drug per cubic centimeter. This concentration is usually effective against the

infecting organism, although higher concentrations may be used if indicated. However, higher concentrations may be irritating to the tissues.

PARKE DAVIS & COMPANY

Solution Tyrothricin 2% W/V 10 cc vials. Each cubic centimeter contains 20 mg of tyrothricin in alcohol 92 per cent.

SHARP & DOHME, INC.

Tyrothricin Concentrate 1 cc ampul of a solution of tyrothricin 25 mg containing 49 cc mercuric borate a solution of tyrothricin accompanied by a diluent.

Cresol and Derivatives

Cresols are phenols in which one of the hydrogen atoms has been replaced by CH_3 . This substitution increases the germicidal efficiency while the toxicity is not increased at least not in the same ratio. The cresols therefore possess distinct advantages as disinfectants. In practice they are much less toxic than phenol because they are used more diluted but they are far from being nonpoisonous. Another advantage of the cresol preparations over phenol is their lower cost. Their disadvantages are the disagreeable odor which depends mainly on impurities, their limited solubility in water and their variable composition and activity.

They may be rendered soluble by the addition of soap as in the official compound solution of cresol and in several other ways. The variability is best discounted by the determination of the phenol coefficient that is the ratio of the germicidal power of the disinfectant to the germicidal power of phenol tested under identical conditions. (The Council has approved the method of the U. S. Public Health Service for determinations of the phenol coefficient. The details of the test are described in *Public Health Reports* July 8, 1921, pp. 1559-1564.) A disinfectant three times as active as phenol against *B. typhosus* would have the coefficient 3 (this being about the coefficient of compound cresol solution). Most disinfectants are now sold with a statement of their coefficient. The degree of dilution for disinfection is obtained simply by multiplying by 20 the phenol coefficient; for instance a disinfectant having the coefficient 3 would be diluted $3 \times 20 = 60$ times.

The official cresol is a mixture of the three isomers of $\text{C}_6\text{H}_4\text{OHCH}_3$. The higher homologues containing two or more methyl groups are generally referred to as cresylic acid. They have a higher disinfectant coefficient.

The toxicity and local actions of the cresols as of other phenols, may be diminished by 'masking' the active OH group through replacement of the H by acid radicals

CRESATIN-Sulzberger (Meta-cresylacetate) — $\text{CH}_3\text{C}_6\text{H}_4\text{O}(\text{CH}_3\text{CO})$ — The acetic acid ester of metacresol $\text{CH}_3\text{C}_6\text{H}_4\text{OH}$

Actions and Uses — Cresatin-Sulzberger is said to possess antiseptic and analgesic properties, and is apparently free from toxic effects. It is said to be useful in the treatment of affections of the nose, throat and ear, such as follicular tonsillitis nasal suppuration due to ethmoid diseases atrophic nasopharyngeal catarrhs, furunculosis of the external auditory canal and purulent otitis media. When applied to mucous membranes it is said to cause no irritation, sloughing or discomfort.

Dosage — Cresatin Sulzberger may be employed either in the pure form or in dilution with oils or alcohol by direct application or spray.

Tests and Standards —

Cresatin Sulzberger occurs as a colorless oily liquid possessing a characteristic odor. It is practically insoluble in water but soluble in the ordinary organic solvents in liquid petrolatum (not over 5 per cent) and in fixed and volatile oils. It is volatile with steam.

0	.	en for one minute with 100 cc
1	.	ter the filtrate has a neutral
2	.	color with ferric chloride solu
3	.	olui on. If 10 cc of cresatin
4	.	no weighable residue

SHARP & DOHME, INC

Cresatin Metacresylacetate (Sulzberger) Supplied in 30 cc glass stoppered bottles

U S patent 1 031 971 (July 9 1912 expired) U S trademark 80 513

Detergents

Cationic

ZEPHIRAN —

mixture of alkyl
the general formu
sents a mixture of

chloride — A
having
repre

Actions and Uses — Zephiran chloride when employed in solutions of the proper dilution is an effective relatively non-injurious surface disinfectant which is germicidal for many pathogenic nonsporulating bacteria and fungi after several minutes' exposure. Solutions of zephiran chloride have low surface tension and possess detergent keratolytic and emulsifying actions, properties which favor penetration and wetting of tissue surfaces. Solutions of ordinary soaps which are anionic detergents in concentrations as low as 0.1 per cent may reduce

the germicidal activity of zephiran chloride, which is a cationic detergent, unless its application is preceded by careful rinsing of soap cleansed areas to be disinfected. Alcohol diminishes the ionization of ordinary soap solution so that the inactivating chemical union of soap with the disinfectant is to some extent prevented. For this reason the application of alcohol 70 per cent (by volume) may well follow the use of the soap and water scrub rinse procedure as carried out in the usual preoperative technic for preparation of the intact skin before application of the disinfectant. Obviously, under such circumstances the use of the tincture is to be preferred, the use of the aqueous solution being restricted to those regions where soap is not ordinarily employed or where alcohol would produce irritation. The careful rinsing of soap also applies to the disinfection of soap cleansed inanimate objects such as surgical instruments.

Solutions of zephiran chloride are said to have an emollient action and to be relatively nonirritating in effective concentrations. Solutions are of comparatively low toxicity under the conditions of use for which they are recommended. Rabbits tolerate from 3 to 5 cc by mouth or 12 cc subcutaneously or intraperitoneally per kilogram of body weight of a 1 per cent aqueous solution. Application to the skin of these animals of various concentrations show that a 0.1 per cent solution is the highest concentration that may be allowed to remain in contact for twenty-four hours without producing irritation. As with other types of disinfectants zephiran chloride has little sporicidal activity and its germicidal potency is greatly reduced by serum. It should be kept in mind that phenol coefficient values as a basis for comparing the relative efficacy of germicides is subject to erroneous interpretation when applied to conditions of actual use.

Zephiran chloride is suitable for general use in the prophylactic disinfection of the intact skin and mucous membranes and in the treatment of superficial injuries and infected wounds in solutions ranging in concentration from 1:40,000 to 1:1,000. It is also used for the preservation of sterilized surgical instruments and rubber articles during storage. Sodium nitrite 0.5 per cent is added to zephiran chloride solutions for the storage of metal instruments to prevent corrosion.

Dosage.—For the preoperative disinfection of the unbroken skin or the treatment of superficial injuries and fungous infections zephiran chloride tincture 1:1,000 (tinted or stainless according to preference) is recommended. Zephiran chloride solution is employed in concentrations of from 1:10,000 to 1:2,000 for the preoperative disinfection of mucous membranes and denuded skin; from 1:5,000 to 1:2,000 for instillation and irrigation of the eye or vagina; and from 1:10,000 to 1:5,000 for widely denuded surfaces. For urinary bladder and urethral irrigation a concentration of not more than 1:20,000 of the aqueous solution is recommended. For retention lavage of the bladder, a concentration not to exceed 1:40,000 should be used.

(50—ec 0.01 N Na₂SO₃) × 0.02143 is not less than 97 per cent nor more than 100 per cent of the original calculated at the dried substance.

[illegible]

WINTHROP CHEMICAL COMPANY, INC.

Zephiran Chloride bulk

Zephiran Chloride Solution 1:1,000 0.24 liter and 38 liter bottles A distilled water solution of zephiran chloride 0.1 per cent

Zephiran Chloride Tincture 1 1,000 (Stainless) 024
liter and 38 liter bottles. An alcohol acetone aqueous solution
containing 0.1 per cent (W/V) zephiran chloride, ethyl alcohol
50 per cent and acetone 10 per cent by volume.

Zephiran Chloride Tincture 1,000 (Tinted) 0.24 liter and 38 liter bottles. An alcohol acetone aqueous solution containing 0.1 per cent (W/V) of zephiran chloride, ethyl alcohol 50 per cent and acetone 10 per cent by volume colored with certified dye (D & C Red No. 39).

U S patents 2 086 585 2 087 131 and 2 087 132 (July 13 1937
expire 1954) and 2 108 765 and 2 113 606 (Feb 15 1938 and April 12
1938, expire 1955) 2 152 047 (March '8 1939 expires 1956) U S
trademark 333 899

Dyes

Dyes are used medically as antiseptics as chemotherapeutic agents and for special effects upon tissue cells. The local antiseptic action of dyes can be explained by their bacteriostatic and bactericidal powers. These are often relatively specific.

The dyes which have been introduced in medicine for the most part in the last decade are practically all organic synthetics. Roughly they may be divided into five classes (1) the azo dyes of which scarlet red medicinal, scarlet red sulfonate and dimazon are described in New and Nonofficial Remedies (these have been in use for considerable time) (2) the acridine dyes such as acriflavine hydrochloride (introduced

as acriflavine), acriflavine base (introduced as neutral acriflavine) and proflavine (3) the fluorescein dyes either as fluorescein or combined with the metal mercury such as mercurochrome soluble and flumerin (4) the phenolphthalein dyes such as phenolphthalein and phenolsulfonphthalein which are official in the U S Pharmacopeia and the chlorine, bromine and iodine substitution products (5) the triphenylmethane or rosaniline series which comprise a large list of substances used in the industries extensively in laboratory practice and more recently in medicine such as gentian violet crystal violet methyl violet and fuchsin, (6) miscellaneous dyes such as methylene blue (methylthionine chloride U S P). Much confusion has existed concerning the composition of dyes various manufacturers of commercial dyestuffs making similar dyes of varying composition both qualitatively and quantitatively usually the commercial dye contains a diluent such as dextrin or salts and is judged by tinctorial power. In order to obtain comparable results when employed clinically the dyes should be of constant composition preferably without diluent.

Azo Compounds

The azo dyes have been used in medicine for many years—more generally recalled under the name scarlet R (scarlet red). The exact constitution of the scarlet R dyes which have been used seems to have varied in minor details with different investigators. Chemically they have been azo compounds (that is they contain the linkage—N=N—) combined with betanaphthol. In New and Nonofficial Remedies a distinction between two scarlet red compounds has been made scarlet red medicinal Biebrich is described as tolylazotolylazo betanaphthol scarlet red sulfonate is described as the sodium salt of azobenzenedisulfonic acid azobetanaphthol, it differs from the former in that the methyl group (CH_3) of tolyl radicals has been replaced by sodium sulfonate ($-\text{SO}_3\text{Na}$) groups. The name Biebrich scarlet red medicinal which occurs in medical literature was erroneously applied in the first place the name Biebrich scarlet is used in dye indexes only for the dye here listed as scarlet red sulfonate.

In addition to the scarlet red compounds there is the chemically related diacetylaminoazotoluene (dimazon) which contains only one azo group and has a diacetylamino [$(\text{CH}_3\text{CO})_2\text{N}-$] group.

Actions and Uses—Scarlet red medicinal Biebrich and scarlet red sulfonate have been claimed to have a marked power of stimulating the proliferation of epithelial cells.

Opinions are divided as to the clinical value but the dyes are used to promote the growth of epithelium in the treatment of burns wounds chronic ulcers etc. In chronic ulcers however it is requisite that the local circulation be good in order to obtain a permanent result.

Dosage—The scarlet red preparations are generally used in the form of an ointment containing from 4 to 8 per cent of the substance. The 8 per cent ointment is somewhat irritating and should be alternated with a soothing ointment. Dimazon is generally used in the form of a 2 per cent ointment, it is also employed as a dusting powder (mixed with talcum) or as a solution (in oil).

SCARLET RED—Sudan IV—Scarlet Red Medicinal—Biebrich Scarlet Red—Aryl azo dye α tolyl azo α tolyl azo β naphthol' *N F*

For description and standards see The National Formulary under Scarlet Red and Ointment of Scarlet Red

Actions, Uses and Dosage—See preceding article Azo Compounds

HEILKRAFT MEDICAL COMPANY

Scarlet Red Salve Scarlet red medicinal 8 parts eucalyptol, 2 parts and petrolatum 90 parts

MERCK & CO., INC

Scarlet Red Medicinal Biebrich (*Powder*) bulk

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Scarlet Red Biebrich Medicinal (*Powder*) bulk

SCARLET RED SULFONATE—Biebrich Scarlet water soluble—The sodium salt of azobenzenedisulfonic acid azobeta naphthol— $C_6H_4(SO_3Na)N=N C_6H_3(SO_3Na)N=N C_{10}H_7OH$

Actions Uses and Dosage—See preceding article Azo Compounds

Tests and Standards—

Scarlet red sulfonate is a dark brownish red odorless powder. It is soluble in water slightly soluble in ether alcohol and acetone almost insoluble in chloroform benzene fixed oils fats and petrolatum.

Add diluted hydrochloric acid to a concentrated aqueous solution of scarlet red sulfonate red floccules separate from the orange red solution. Add sodium hydroxide solution to a concentrated aqueous solution of the substance a brownish red precipitate forms. Treat the substance with concentrated sulfuric acid a green solution results which becomes blue on the addition of water and on further dilution brownish red floccules separate. Dissolve about 0.1 Gm. of the substance in 5 cc. of glacial acetic acid heat to boiling add zinc dust and continue the boiling the liquid becomes almost colorless.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Scarlet Red Sulfonate (*Powder*) bulk

PARKE DAVIS & COMPANY

Scarlet Red Emulsion 4 per Cent Scarlet red sulfonate
4 parts alcohol 4 parts sterilized quince seed jelly 92 parts

Scarlet Red Ointment 5 per Cent Scarlet red sulfonate
5 parts petrolatum containing a small amount of wax 95 parts

Scarlet Red Ointment 10 per Cent Scarlet red sulfonate
10 parts petrolatum containing a small amount of wax 90 parts

Acridine Derivatives

The acridine derivatives are mostly yellow dyes—acridine dyes obtained from coal tar—to which the term flavine has been applied (flavine should more correctly be applied to a vegetable coloring matter). The representative acridine dyes used in medicine are acriflavine hydrochloride (introduced as trypaflavine and acriflavine) acriflavine base (introduced as neutral trypaflavine and neutral acriflavine) and proflavine. In 1912 Ehrlich found that the acridine dye diaminomethylacridinium chloride hydrochloride possessed therapeutic properties when used in trypanosome infections and hence he termed it *trypaflavine*. Later this substance was investigated in England particularly in regard to its effects as a wound antiseptic and the name acriflavine was applied to it. In a generic sense the terms trypaflavine and acriflavine have been applied both to acriflavine base and acriflavine hydrochloride. Another closely related substance diaminoacridine monohydrogen sulfate was studied also to which was given the name proflavine. A considerable number of bacteriologic and clinical reports on these substances have been published. It appears to be established that these dyes possess marked antiseptic and germicidal properties and on this account they have been employed in a number of pathologic conditions. Acriflavine and proflavine compounds are manufactured under U. S. patent 1,005,176 (Oct. 10, 1911 expired) by license of the Chemical Foundation Inc.

Actions and Uses.—The antiseptic or bacteriostatic action of acriflavine hydrochloride and proflavine appears to be weakened in the presence of serum. In the treatment of wounds it is claimed that these drugs are comparatively free from toxic or irritant action on living tissues and that they do not inhibit appreciably the phagocytic action of the leukocytes. Acriflavine hydrochloride is claimed to exert a specific bactericidal action on the gonococcus. The evidence indicates that it has a greater antiseptic action than proflavine though its action is slower. Applications of acriflavine hydrochloride, acriflavine base and proflavine have been employed in the treatment of wounds, urethritis, gingivitis, gonorrheal conjunctivitis, blenorria, eczema.

furunculosis otitis media, and other conditions requiring the use of a germicide. When taken by mouth the dyes tend to render the urine antiseptic provided the reaction of the secretion be alkaline. The use of acriflavine base rather than acriflavine hydrochloride has been suggested in areas where freedom from irritation (due to the acid reaction of acriflavine hydrochloride and proflavine) is desirable. The intravenous use of acriflavine base has been proposed, but critical evidence for its necessity is lacking.

Dosage—In the treatment of wounds the solution generally employed is 1 in 1,000 in physiological solution of sodium chloride, although weaker solutions may be used. In suppurating wounds, this solution is used for syringing and swabbing the wound after free incision, for irrigation after providing adequate drainage, and for saturating the gauze with which the wound is finally covered. Evaporation should be prevented by protective dressing. In cavities gauze saturated with the solution may be used as a light packing. Fresh wounds are cleansed thoroughly with the solution and as much of the solution as possible is left in contact with the injured surfaces. Such wounds may be closed by suture and may be expected to heal by first intention.

In the treatment of open wounds, an ointment has been used which contains 1 per cent of proflavine oleate (prepared from proflavine base) in an ointment base composed of equal parts of petrolatum and calcium carbonate. A thick layer of the ointment may be spread on gauze and applied to the surface of the cleansed wound, or the ointment may be spread on the wound directly. The primary dressing need not be changed for several days.

In gonorrhea a strength of 1 in 1000 in isotonic solution of sodium chloride may be used for injection into the urethra. For irrigation when relatively large quantities are to be used a 1 in 4000 solution is preferable because it is less irritating; solutions of from 1 in 6000 to 1 in 10000 have been used. In throat infections a spray of 1 in 1000 solution is used. In middle ear suppurations a 1 in 500 solution in 50 per cent alcohol is dropped into the ear or the cavity may be packed with gauze wet with the solution. In gingivitis the mouth is irrigated with a 1 in 1000 solution. Solutions of acriflavine hydrochloride, acriflavine base and proflavine may be boiled, or heated in an autoclave to 130° C., without decomposition but they are sensitive to light and should be stored in amber bottles. Solutions over a week old should be discarded.

ACRIFLAVINE—Acriflavine Base—Neutral Acriflavine—“A mixture of 2, 8 diamino 10 methylacridinium chloride and 2, 8 diaminoacridine containing, when dried to constant weight at 100° C. not less than 13.3 per cent and not more than 15.8 per cent of Cl” *N F*

For description and standards see the National Formulary under Acriflavine

Actions, Uses and Dosage—See preceding article, Acridine Derivatives

ABBOTT LABORATORIES

Acriflavine (Powder): bulk

Enterab Acriflavine Tablets: 30 mg Each tablet is enteric coated with a resin prepared from stearic acid phthalic anhydride and glycerine

U. S. trademark 353 674

Tablets Acriflavine: 0.1 Gm One tablet dissolved in 100 cc of isotonic solution of sodium chloride makes a 1:1,000 solution

Tablets Acriflavine: 30 mg One tablet dissolved in 30 cc of isotonic salt solution makes a 1:1,000 solution

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Acriflavine (Neutral) (Powder): bulk

Acriflavine (Neutral) "Pro Injections": 0.5 Gm and 10 Gm vials

Enteric Coated Tablets Acriflavine (Neutral): 324 mg Each tablet is coated with phenyl salicylate containing some keratin

Tablets Acriflavine (Neutral): 0.1 Gm

Acriflavine (Neutral) Troches: Each troche contains neutral acriflavine, 6 mg; menthol, 0.6 mg and sodium chloride, 0.6 mg

Ointment Acriflavine (Neutral), 1 Per cent: Acriflavine 1 part, dissolved in glycerin 8 parts, and incorporated with a base composed of hydrous wool fat and petrolatum to make 100 parts

ACRIFLAVINE HYDROCHLORIDE — A mixture of the hydrochlorides of 2, 8 diamino-10 methylacridinium chloride and 2, 8 diaminoacridine containing, when dried to constant weight over sulfuric acid, not less than 23 per cent and not more than 24.5 per cent of Cl. *N. F.*

For description and standards see the National Formulary under Acriflavine Hydrochloride

Actions, Uses and Dosage—See preceding article, Acridine Derivatives

ABBOTT LABORATORIES

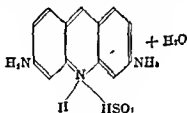
Acriflavine Hydrochloride (*Powder*): bulk.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Acriflavine Hydrochloride (*Powder*): bulk. Controlled biologically so that the maximum nonlethal dose for mice weighing 20 Gm. shall not exceed 15 mg.

To determine the maximum nonlethal dose the drug is dissolved in water in such concentration that 1 cc. contains the quantity to be administered. A series of mice weighing 20 Gm. each are injected subcutaneously with small doses of the drug, each succeeding animal receiving an increase of $\frac{3}{10}$ mg. of the drug over the preceding one. The dosage under which all of the animals survive and over which all die is the maximum nonlethal dose.

PROFLAVINE. — Proflavina. — Proflavine Sulfate. — 2, 8-diaminoacridinium monohydrogen sulfate.



Actions, Uses and Dosage—See preceding article, Acridine Derivatives

Tests and Standards—

Proflavine is a reddish brown odorless, crystalline powder. It is soluble in water and in alcohol, forming brownish solutions which fluoresce on dilution; it is nearly insoluble in ether, chloroform, liquid petrolatum, fixed oils and volatile oils.

An aqueous solution of proflavine is neutral to litmus. Add a few drops of hydrochloric acid to an aqueous solution of proflavine which is sufficiently dilute to be fluorescent; the fluorescence disappears but partially reappears on dilution with water. Add 2 drops of sulfuric acid to about 1 cc. of an aqueous solution of proflavine (1 in 250), and agitate the mixture. Under the microscope, matic needles. An aqueous solution precipitate with barium chloride. An aqueous solution of proflavine silver nitrate solution (*distinct* of formaldehyde solution to 5 c (1 in 250), and immediately a (1 in 10). A violet color is produced with sodium nitrite solution, a brown color after a few minutes, which becomes observed after which becomes (250) gives a *distinct* precipitate weighed the ash amounts to.

Dissolve about 1 Gm of proflavine accurately weighed in 250 cc of warm water collect the insoluble matter if any in a weighed Gooch crucible wash the insoluble matter with hot water dry and weigh the residue the insoluble matter amounts to not more than 1 per cent
Dry about 1 Gm of proflavine accurately weighed to constant weight at 100 C the substance loses not more than 10 per cent of its weight

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Proflavine (Powder): bulk Controlled biologically so that the maximum nonlethal dose for mice weighing 20 Gm does not exceed 6 mg

To determine the maximum nonlethal dose the drug is dissolved in water in such concentration that 1 cc contains the quantity to be administered Of a series of mice weighing 20 Gm apiece each is injected subcutaneously with small doses of the drug each succeeding animal receiving an increase of $\frac{1}{10}$ mg of drug over the preceding one The dosage under which all of the animals survive and over which all die is the maximum nonlethal dose

Triphenylmethane (Rosaniline) Derivatives

Of the derivatives of triphenylmethane and its homologue polydiphenylmethane, the most interesting medicinally are those which result from the introduction of amino groups forming pararosanine $(\text{NH}_2\text{C}_6\text{H}_4)_2\text{COH}$
with hydrochloric

the formation of a quinoid group, thus is formed a typical dye known as fuchsin $\text{NH}_2\text{C}_6\text{H}_4\text{CH}_2\text{NH}_2\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{NH}_2\text{Cl}$ The red color of pararosanine chloride or fuchsin is changed to violet by the entrance of a methyl group in the amino groups the intensity of the violet color increasing with an increasing number of methyl groups Thus, there are the closely related gentian violet, crystal violet and methyl violet Gentian violet is hexamethylpararosanine chloride with an admixture, usually of pentamethylpararosanine and tetramethylpararosanine chlorides, by some it is defined as a mixture of methyl violet and crystal violet Crystal violet is a relatively pure form of hexamethylpararosanine chloride methyl violet is considered to contain the same as the same as will be found that there is little difference between the penta and hexa derivatives and the mixtures of the two, so that the one most easily obtained in pure form (crystal violet) will be the one most used The material which has been used by the workers so far however, has been gentian violet

Actions and Uses—Gentian violet was introduced as an antiseptic by J Stelling in 1890 and has been advocated by Churchman who found that solutions of the dye had a selective

action on certain bacteria and that the majority of gram negative organisms survived exposure to gentian violet solutions in strengths far in excess of that required to kill gram positive organisms, in fact, the action of the dye is sufficiently selective so that often a strain within a species is not affected. Churchman's work, however, was done largely with a product containing dextrin as a diluent. Gentian violet is a useful antiseptic for infected wounds, mucous membranes and serous surfaces. Its chief application has been in the treatment of affections of the pleural cavity and of the joints, particularly in empyema and arthritis—affections in which staphylococci, *Ps. aeruginosa* and *C. diphtheriae* are the causative agents. Evidence has been advanced that gentian violet administered in enteric coated tablets, is of value as an anthelmintic in the treatment of *Strongyloides* infestation. Churchman also has found that acid fuchsin (the acid sodium salt of fuchsin disulfonic and trisulfonic acids) is in some respects the opposite of that of gentian violet in selective power, a stained culture of *Ser. marcescens* (*prodigiosus*) being killed by the acid fuchsin, while the gram positive *B. anthracis* would be unaffected. The selective action of acid fuchsin, however, is clearly brought out only when the organisms are exposed to the dye with slight elevation of temperature (about 50 C). Acid fuchsin is incompatible with gentian violet and the compatibility of all mixtures of dyes should be determined before any combination is prepared. Churchman claimed, however, that aeriflavine possesses much the same selectivity as acid fuchsin, so he proposed the use of a mixture of these two dyes. The effectiveness of such a solution has not yet been established clinically. None of the rosaniline dyes is a strong bactericide.

GENTIAN VIOLET MEDICINAL—Methylrosaniline chloride U. S. P.—Methyl Violet—Crystal Violet—"Hexa methylparaosaniline usually admixed with pentamethylparaosaniline chloride and tetramethylparaosaniline"—U. S. P.

For standards see the U. S. Pharmacopeia under Methylrosaniline Chloride.

Actions and Uses—See preceding article Triphenylmethane (Rosaniline) Derivatives.

Dosage—60 mg. U. S. P. For direct application a solution of from 1 in 500 to 1 in 1000 may be employed, for instillation, a 1 in 10000 solution.

THE COLEMAN & BELL COMPANY, INC.

Gentian Violet Improved Medicinal (Powder) bulk
Gentian violet medicinal

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

Gentian Violet Medicinal (*Powder*) bulk

Tablets Gentian Violet Medicinal 32.4 mg

Enteric Coated Tablets Gentian Violet Medicinal 32.4 mg The tablets are coated with phenyl salicylate containing some keratin

Formaldehyde

The antiseptic actions of formaldehyde cannot be utilized directly on the body because of the irritant and coagulant effects. Attempts have been made to avoid these effects by combining the formaldehyde in such a way as to cause it to be liberated very gradually. The results have been rather disappointing because it is difficult if not impossible to secure just that degree of stability in which the formaldehyde will be liberated in concentrations sufficient to maintain the antiseptic action but not sufficient to become irritant. Methenamine (hexamethylenetetramine) is a notable exception but its effects are confined to acid fluids and therefore essentially to the urine. Other compounds are effective mainly through the other constituents with which the formaldehyde is combined rather than through the formaldehyde itself.

The wide reactivity of formaldehyde gives the possibility of a great variety of compounds, with proteins, carbohydrates, amides, phenols and aromatic derivatives. Methenamine does not contain formaldehyde as such but liberates it under certain conditions (See systemic anti-infectives).

SOLUTION OF FORMALDEHYDE—U S P—Formalin.—An aqueous solution containing not less than 37 per cent of CH_2O with variable amounts of methanol to prevent polymerization. **U S P**

For description and standards see the U S Pharmacopeia

Actions Uses and Dosage—See Useful Drugs

MERCK & CO INC

Solution Formaldehyde bulk

Halogen Compounds

Chlorine Derivatives

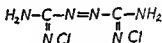
The germicidal action of free chlorine and the hypochlorites is well known. In medicine this action has been utilized by the employment of chlorine water chlorinated lime and alkaline

solutions of sodium hypochlorite (Labarraque's solution) and potassium hypochlorite (Javelle water)

Hypochlorite preparations are fairly stable in the presence of alkali, and alkaline hypochlorite preparations have the added advantage that the alkali has a destructive and solvent action on most bacteria and other organic matter. In the treatment of infected wounds with hypochlorite solutions, an excessive degree of alkalinity is held to be objectionable on the grounds that it causes destruction of normal tissue and irritation of the skin.

On the theory that the action of hypochlorites is dependent on the combination of their active chlorine ($\text{Cl}+$) with the nitrogen of protein, certain organic preparations containing a chloramid group, which are practically neutral and relatively stable, have been proposed as substitutes.

CHLORAZODIN—Azochloramid—'Contains the equivalent of not less than 37.5 per cent and not more than 39.5 per cent of active chlorine (Cl)'—U S P



For description and standards see the U S Pharmacopœia under Chloroazodin and Solution of Chloroazodin.

Actions and Uses—Similar to those of a dilute solution of sodium hypochlorite, chloramine T and of dichloramine T except that it does not hydrolyze appreciably in aqueous solutions and that its rate of reaction with mild reducing agents and organic matter in general is low. Consequently, its concentration does not decrease rapidly and it is claimed that it exerts a more prolonged and stronger bactericidal action in the presence of tissue fluids and exudate than the other chloramines. Solutions of chloroazodin are used on dressings for wounds and on packings for infected cavities. Aqueous solutions are suitable for lavage of wounds, and for irrigations of and instillations into cavities. It is claimed that short exposure of epithelial tissue to aqueous solutions is harmless and that solutions of chloroazodin in vegetable oil (1:2000) are applicable to the mucous membrane of the vagina, colon, and rectum. The available evidence indicates that chloroazodin possesses relatively low toxicity and is a relatively nonselective bactericidal agent.

Dosage—Chloroazodin is usually employed in wounds in a dilution of 1:3300 in an approximately isotonic solution buffered at pH 7.4. Greater dilutions up to 1:3200 are proposed for use on mucous membranes. On dressings and packings the stable solution containing 1 part of chloroazodin in 500 parts of glyceryl triacetate (triacetin) is used. Gauze impreg-

nated with the triacetin solution of chloroazodin does not dry out and does not stick to the wound. A solution prepared by mixing one volume of a strong solution of chloroazodin in triacetin (1 125) with 19 volumes of a vegetable oil contains one part of chloroazodin in 2000 parts (by weight) of the solution and is claimed to be sufficiently bland to be applicable to certain mucous membranes.

WALLACE & TIERNAN PRODUCTS, INC

Saline Mixture of Azochloramid—This contains Azo chloramid 3.17 per cent sodium chloride 89.56 per cent, mono potassium phosphate 0.93 per cent and sodium phosphate exsicc. 6.32 per cent by weight. Bottles of the powder containing 35.93 Gm. for preparing 1 gallon and bottles of the powder containing 1800 Gm. for preparing 50 gallons of aqueous solution of Azochloramid (1 3,300)

Saline Mixture Tablets of Azochloramid—Each tablet contains 0.55 Gm. of the Saline Mixture of Azochloramid for preparing 60 cc. of the aqueous solution of Azochloramid (1 3,300)

Surface Active Saline Mixture of Azochloramid 47 Gm. envelopes. Each envelope containing azochloramid 0.14 Gm. sodium tetradecyl sulfate 0.47 Gm. and buffered saline mixture 4.09 Gm. for the preparation of 473 cc. of isotonic solution.

Surface Active Saline Mixture of Azochloramid 37.85 Gm. bottles each containing azochloramid 1.16 Gm. sodium tetradecyl sulfate 3.79 Gm. sodium chloride 30.55 Gm. mono potassium phosphate 0.30 Gm. and anhydrous sodium phosphate 2.05 Gm.

Solution of Azochloramid in Triacetin (1 500)—A solution containing chloroazodin 1 Gm. in 500 Gm. of triacetin. Triacetin is a mixture of glyceryl acetates containing approximately 95 per cent of glyceryl triacetate.

Strong Solution of Azochloramid in Triacetin (1 125)—A solution containing chloroazodin 1 Gm. in 125 Gm. of triacetin for use in the preparation of chloroazodin in vegetable oil (1 2000)

CHLORAMINE T—Chloramine—Chloramine T contains the equivalent of not less than 11.5 per cent and not more than 13 per cent of active chlorine (Cl). U. S. P.

For description and standards see the U. S. Pharmacopeia under Chloramine T.

Actions and Uses—The actions of chloramine T are essentially similar to those of diluted solution of sodium hypochlorite.

U S P It has the advantage of greater stability, convenience of preparation, and the production of less irritation. On the other hand, it lacks the solvent action of alkaline hypochlorites.

It is practically nontoxic, but should not be used by mouth, since it is decomposed by the gastric juice.

Dosage—Chloramine-T is used in 0.1 to 4 per cent aqueous solution. For wounds, the normal strength is from 1 to 2 per cent, applied by the same technic as the surgical solution of chlorinated soda. It has also been employed for irrigation of the urethra, bladder and uterus, and as a mouth wash.

ABBOTT LABORATORIES

Chlorazene (Powder): 378 Gm, 189 Gm, 113 Gm and 56 Gm bottles. Chloramine-T.

Aromatic Chlorazene Powder: 454 Gm and 227 Kg bottles. Chloramine-T, 5 per cent, sodium bicarbonate, 5 per cent, eucalyptol, 2 per cent, saccharin, 1 per cent, sodium chloride, 87 per cent.

Tablets Chlorazene: 0.3 Gm

U S trademark 119 014

DICHLORAMINE-T.—Dichloramine—"Paratoluenesulfondichloramide contains the equivalent of not less than 28 per cent and not more than 30 per cent of active Cl." *N F*

For description and standards see the National Formulary under Dichloramine-T.

Actions and Uses—Dichloramine-T is an effective germicide through its content of active chlorine (Cl⁺). It is only sparingly soluble in water, but soluble in chlorinated eucalyptol or chlorinated paraffin (chlorcosane). The solution produces a gradual, sustained antiseptic action.

It is more irritant than chloramine, but also more solvent. It should not be administered internally.

Dichloramine T is claimed to be useful in the prevention and treatment of diseases of the nose and throat, it has been used with success when applied to wounds.

Dosage—Dichloramine T dissolved in chlorinated paraffin (which see) is used in concentrations of from 0.5 to 10 per cent. In nasopharyngeal work from a 1 to a 2 per cent solution is employed, for application to wounds a 5 per cent solution. The solution of dichloramine T in chlorinated paraffin is not very stable and should not be kept for more than two or three days. At times the solutions may become irritating to the skin because of the formation of hydrochloric acid. Both dichloramine-T powder and solution should be protected from sunlight to prevent decomposition.

ABBOTT LABORATORIES

Dichloramine-T (Powder): bulk

HALAZONE — *p* sulfonedichloramidobenzoic acid —
 $C_6H_4(SO_2NCl_2)COOH$ 14

Actions and Uses—Halazone is said to be a powerful disinfectant. It is said to act like chlorine, but to have the advantage of being stable in solid form. In the presence of alkali carbonate, borate and phosphate, Dakin and Dunham report that, in from thirty to sixty minutes halazone in the proportion of from 1 in 200 000 to 1 in 500 000 sterilized polluted water contaminated with such organisms as *Bacterium coli*, *Bacterium typhosum*, *Bacterium paratyphosum* A and B, *Vibrio cholerae* and *Bacterium dysenteriae*.

Dosage—For the sterilization of water, 4 to 8 mg of halazone, in the form of tablets containing sodium carbonate (or sodium borate) and sodium chloride, is added to 1 liter

Tests and Standards—

1. A solution of 0.1 Gm of halazone in 100 cc of water is prepared by H. D. Dakin and J. C. Dunham (J. Biol. Chem. 201 1917) under conditions of chlorine. It is stable in the presence of petroleum ether, and the formation of a white precipitate in stout prisms of sodium chloride is 213 C.

2. Halazone tablets containing 110 mg of sodium carbonate and sodium chloride from a sodium bromide solution.

If 15 cc of a saturated aqueous solution of aniline is treated with

10 cc of a 10 per cent solution of sodium hydroxide, the mixture is then acidified with acetic acid and titrated with tenth normal sodium thiosulfate solution. The theoretical chlorine content of pure halazone is 26.26 per cent.

About 0.15 Gm of halazone (or in the case of halazone tablets 30 tablets), accurately weighed, is dissolved in from 50 to 100 cc of water and 10 cc of a 10 per cent sodium hydroxide solution. Fifteen cc of a 10 per cent potassium iodide solution is added and the mixture is then acidified with acetic acid and titrated with tenth normal sodium thiosulfate solution.

The theoretical chlorine content of pure halazone is 26.26 per cent. The theoretical chlorine content of pure halazone is 26.26 per cent.

ABBOTT LABORATORIES

Halazone (Powder): bulk

Tablets Halazone—Halazone, 4 mg, sodium borate, 11 mg and sodium chloride sufficient to make about 0.13 Gm

HYCLORITE—A solution of chlorinated soda, each 100 Gm of which is stated to contain sodium hypochlorite 4.05 Gm, sodium chloride 250 Gm, calcium hydroxide 0.14 Gm, inert salts 0.65 Gm. It contains not less than 3.85 per cent of available chlorine.

Actions and Uses—Hyclorite differs from solution of chlorinated soda-U S P, chiefly because of the greater content of available chlorine and the lesser degree of alkalinity of the former. It has the actions and uses of solution of chlorinated soda-U S P, and when properly diluted it also may be used in the same conditions as those for surgical solution of chlorinated soda U S P. One volume of hyclorite diluted with 7 volumes of water has the same available chlorine content as surgical solution of chlorinated soda, and is isotonic.

Dosage—Hyclorite is used full strength or diluted with 1 or 2 parts of water for direct application to mucous membrane, muscular tissue, bone infections, etc. For irrigation of wounds, throat and body cavities, dilutions of from 1 in 200 to 1 in 2000 are used. For use in the irrigation method of treating infected wounds, dilute 1 part of hyclorite with 7 parts of water.

The available chlorine content of hyclorite decreases at the rate of about 12 per cent per year. In order that due allowance for this decrease may be made when diluting for use, each bottle of hyclorite bears the date of bottling.

Tests and Standards—

Hyclorite is prepared by decomposing chlorinated lime suspended in water with sodium carbonate.

Hyclorite has the properties of solution of chlorinated soda U S P, but contains no carbonate. When exposed to air a pellicle forms on its surface owing to the formation of calcium carbonate.

To about 5 grams of hyclorite accurately weighed add 50 cc of distilled water. To the resulting solution slowly add 10 cc of a 3 per cent hydrogen peroxide solution previously rendered neutral. After the reaction is completed as indicated by the cessation of the evolution of the oxygen, 4 drops of methyl orange indicator solution and an excess (measured) of tenth normal hydrochloric acid are added. Titrate the residual acidity with tenth normal sodium hydroxide; the alkalinity found corresponds to not more than 0.14 Gm of calcium hydroxide per 100 Gm of hyclorite.

Mix in a flask about 5 cc of hyclorite accurately weighed with 50 cc of distilled water, add 1 Gm of potassium iodide and 5 cc of acetic acid and titrate with tenth normal sodium thiosulfate, starch test solution being used as indicator. It shows not less than 3.85 per cent of available chlorine.

Each cc of tenth normal sodium thiosulfate used corresponds to 0.003546 Gm of available chlorine. Due allowance should be made for a decrease in available chlorine content of about 12 per cent per year calculated from the date of bottling stamped on each bottle.

PENNSYLVANIA SALT MANUFACTURING CO
(Bethlehem Laboratories Inc., Distributor)

Hyclorite (Solution) bulk
U S trademark 120 110

SUCCINCHLORIMIDE — N-chlorosuccinimide — The chlorinated imide of succinic acid— $C_4H_4O_2NCl$ —M W 133.54 Succinchlorimide yields not less than 25.0 per cent nor more than 26.6 per cent of active chlorine



Actions and Uses—Succinchlorimide is proposed for use in disinfection of water. Data were submitted showing that succinchlorimide will disinfect water containing *Escherichia coli*, *Eberthella typhi*, *Salmonella paratyphi* A and B, *Vibrio cholerae* and *Shigella dysenteriae* within twenty minutes in dilution of 1:16 parts per million (approximately 1:100,000).

Dosage—For the disinfection of water, 11.6 mg of succinchlorimide per liter.

Tests and Standards—

begins to sublime at about 127°C and melts at from 145 to 150°C.

Although it appears to be relatively stable toward light and air at ordinary temperatures, succinchlorimide should be packaged in air-tight, light-resistant containers.

1. Weigh 2.0 g of succinchlorimide in a 100-ml volumetric flask and add 2 cc

than 0.15 per cent.

flask and shake it frequently and vigorously, with care to avoid loss of contents. Each cubic centimeter of tenth normal sodium thiosulfate is equivalent to 0.001773 Gm of active chlorine. The active chlorine content of succinechlorimide is not less than 25.0 per cent nor more than 26.6 per cent.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORP.

Succinechlorimide* Bulk

Iodine and Iodine Derivatives

Certain iodine compounds are used for their local irritant and antiseptic effects, which are due probably to the action of free iodine contained in the preparations or liberated from them, or they may be administered for their systemic actions and for roentgen ray diagnosis.

Iodine Preparations Containing Free Iodine

IOCAMFEN—A liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine.

Actions and Uses—Iocamfen has the antiseptic and germicidal properties of iodine and the analgesic and stimulating properties of camphor and phenol.

Iocamfen is used especially in the treatment and dressing of wounds, and in dentistry, also in ringworm of the feet, nails and other parts of the body.

Dosage—Iocamfen is applied in small quantities directly to wounds, the skin, cavities, etc., or on tampons or drainage material.

Tests and Standards—

Iocamfen is a dark reddish brown viscous liquid having a camphoraceous odor. It is insoluble in water, but soluble in all proportions in alcohol, ether, benzene and liquid petrolatum.

Iocamfen like free iodine interacts with fats and waxes; its free iodine entering into combination.

About 2 Gm iocamfen is weighed into a glass stoppered flask and dissolved in about 25 cc of chloroform. Add about 10 cc of potassium iodide solution (1 in 10) and titrate the free iodine by shaking with tenth normal sodium thiosulfate solution using starch solution as an indicator.

SCHERING & GLATZ, INC

Iocamfen (Liquid): 30 Gm and 113 Gm bottles

U. S. trademark 112,934

Iodine Dusting Powders

Dusting powders containing iodine in various combinations are used in the treatment of wounds, granulating surfaces, abscess cavities, etc. The clinical results are ascribed to a slight anti-

septic action of the iodine to stimulation of phagocytosis and to diminished secretion from the wound which renders it a less favorable culture medium for germs

Iodoform has been the standard drug of this class. Other insoluble organic iodine compounds have been introduced to replace iodoform but with limited success. While they avoid the disagreeable odor and the occasional toxic systemic effects they also lack much of the efficiency

THYMOL IODIDE—A mixture of iodine derivatives of thymol principally dithymoldiiodide $[(C_6H_7CH_2C_6H_7OI)_2]$ containing, when dried over sulfuric acid for 18 hours, not less than 43 per cent of I" *U S P*

For description and standards see the U S Pharmacopeia under Thymol Iodide

MERCK & Co, INC

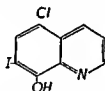
Thymol Iodide (*Powder*) bulk

WINTHROP CHEMICAL COMPANY, INC

Aristol (*Powder*) Thymol iodide 30 Gm bottle

U S trademark 17 393

VIOFORM—5 chloro 7 iodo-8-hydroxyquinoline — C_8H_6N
 $OHICl$ —A substitution compound of 5 chlor 8 hydroxyquinoline resulting from the introduction of one atom of iodine



Actions and Uses—Vioform is used as an almost odorless substitute for iodoform. It is also employed against trichomonas vaginitis and internally against amebiasis. It is used in atopic dermatitis, eczema of the external auditory canal, eczema of the legs, scalp, scrotum and perineum, also in chronic dermatitis, oil dermatitis, acute psoriasis and intertriginous psoriasis.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endameba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa. Positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is

considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases. In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes re examinations and repetitions of courses of treatment.

Dosage—Vioform is used as a dusting powder for application to wounds, ulcers, burns, exudative skin eruptions, etc. It is also used externally as a 2 per cent to 3 per cent ointment, lotion or paste. Against amebiasis 0.75 Gm to 1.0 Gm daily (in capsules in divided doses of 0.25 Gm by mouth for 10 days, with repetition of the course after a rest period of a week to ten days. A few cases of gastro intestinal irritation with this dosage have been reported, on account of the high iodine content. Until more with caution

Caution—Vioform used locally stains linen yellow on contact

Tests and Standards—

Vioform is a grayish yellow powder, having a very faint aromatic odor, almost insoluble in water, sparingly soluble in alcohol, soluble in hot glacial acetic acid.

Boil a specimen of vioform with dilute hydrochloric acid; it dissolves slowly, evolving an odor of iodine. Treat a specimen of vioform with concentrated sulfuric acid; copious vapors of iodine are evolved. Repeatedly crystallize vioform from hot glacial acetic acid; crystals are obtained which melt at 173 to 180 C.

Mix about 0.5 Gm of vioform, accurately weighed, in nickel crucible with a mixture of powdered sodium hydroxide 4 parts and potassium nitrate 1 part, and heat until fusion has been completed. Cool and dissolve the fused mass in 150 cc of water, warming to hasten solution, filter into a 400 cc beaker and wash well. Add 25 cc of tenth normal silver nitrate (the amount of silver is k in the formula below), then add slowly, to litmus paper. Filter, wash and titrate the excess normal potassium sulfocyanate. The precipitate in the iodide with some silver alcohol then with ethyl amount of iodine can be

$$x = \frac{0.7527 w + a - k}{293}$$

where w equals combined weight of silver iodide and silver chloride; x equals weight of silver iodide and $(w-x)$ equals weight of silver chloride by this method. Vioform contains not less than 37.5 per cent nor more than 41.5 per cent of iodine, and not less than 11.5 per cent or more than 12.2 per cent of chlorine.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Vioform (Powder): bulk

Tablets Vioform: 250 mg

Vioform Insufflate 30 Gm and 248.8 Gm bottles contain ing vioform 25 per cent boric acid 10 per cent zinc stearate 20 per cent lactic acid $2\frac{1}{2}$ per cent and lactose $42\frac{1}{2}$ per cent

Vioform Vaginal Inserts Each insert contains vioform 250 mg lactic acid 25 mg boric acid 100 mg and diluent to make 2 Gm.

U S patent 641 491 (Jan 16 1900 exp red) U S trademark 92 732

Isoparaffinic Acids

ISO PAR—A mixture of water insoluble isoparaffinic acids partially neutralized with iso-octyl hydroxybenzyl-dialiphatic amines. The water insoluble isoparaffinic acids are obtained by oxidation of petroleum hydrocarbons by the passage of a current of oxygen under pressure at an elevated temperature in the presence of a metallic catalyst. The water insoluble monocar-

5 carbon atoms

The hydroxy

with the iso-

latter is then

used by distillation

Actions and Uses—Unguentum Iso Par is for external use only. It should not be covered with thick tight bandaging since irritation may result from this type of dressing. It is said to be of value in the treatment of pruritus ani and vaginae, mycotic infections of the hand and feet and eczemas of the ear and certain skin allergic manifestations. This ointment is stimulating lowers the levels of irritability of the skin and is in varying degrees bactericidal and fungicidal.

Dosage—It should be applied with a rubber finger stall a small wad of absorbent cotton or gauze or other convenient applicator since it possesses an odor which may be objectionable if it persists on the fingers. The first applications may cause a temporary burning sensation but this disappears later. The ointment should be applied to the affected area in the evening before retiring and again in the morning if necessary it may be applied more frequently. It is claimed that the majority of cases will show evidence of response within three to five days possibly up to two weeks. If by that time relief is not obtained some other form of treatment should be substituted.

Tests and Standards—

Iso-Par is a viscid dark brown oily liquid having a characteristic odor of burnt petroleum. It is immiscible with water freely miscible with alcohol volatile oil and fixed oil. The specific gravity is from 0.970 to 0.980 at 25 C.

Place about 2 cc. of iso-par in a glass stoppered cylinder add 20 cc. of water shake the contents for five minutes filter through moistened paper and divide into two portions to one portion add two drops of methyl red test solution a distinct red color persists to the other portion add two drops of thymol blue test solution a distinct yellow color persists.

MEDICAL CHEMICALS, INC

Unguentum Iso-Par 14 Gm, 28.5 Gm, 114 Gm. and 454 Gm jars Contains Iso-Par 17 per cent and titanium dioxide 4 per cent in an ointment base consisting of beeswax, cetyl alcohol, lanolin and petrolatum

U S patent 2 262 720 (expires 1958) U S trademark 365 069

Metal Compounds

Bismuth

The insoluble compounds of bismuth are used for their mechanical action as protectives of inflamed or irritated surfaces. On a wound a firm crust is formed, beneath which healing proceeds. The drying property of the powder is of chief importance, and the antiseptic action secondary. For the best development of the protective mechanical action a very fine division of the bismuth compound is essential. This has been secured in various ways. Soluble complex salts of bismuth, which are decomposed by dilute mineral acids with precipitation of insoluble bismuth salts in a very fine state of subdivision, are administered with the expectation that the gastric juice will bring about precipitation and thus protect the digestive tract. It is questionable whether this assumption is realized in many cases. Pharmacologists and many clinicians doubt the usefulness of all soluble bismuth preparations as a means of securing their protective action. On the other hand, the powder is given alone or prepared in a permanent suspension holding the bismuth in such a fine state of division as to favor its deposition evenly throughout the whole intestinal tract.

Bismuth has been combined with other substances, either in mixture or in synthetic compounds, to produce insoluble compounds which shall be useful as a means of securing convenient administration or of enhancing protective and antiseptic actions. It is doubtful whether combination with antiseptic acids as in bismuth subgallate or bismuth subsalicylate, increases the efficiency of the preparation. The antiseptic acids lose their power in alkaline liquids as in the intestines, the introduction of iodine into the benzene nucleus does not increase the antiseptic power. On the other hand, bismuth compounds with phenol or with phenols in which bromine or iodine has replaced hydrogen in the benzene ring have an antiputrefactive action.

Soluble compounds of bismuth used for their protective action should be employed with caution because of the danger of absorption of poisonous amounts of bismuth. Absorption of insoluble bismuth compounds from wounds and cavities occasionally occurs. Skin lesions similar to those sometimes following the use of arsphenamine are among the most important complications of bismuth therapy. For example a pruritus, an erythema, an urticaria or a dermatitis and rarely hemorrhagic lesions are noted following bismuth therapy, and cases of

agranulocytosis with angina have been reported. The administration of the drug should be stopped on the first sign of cutaneous irritation. Bismuth poisoning is indicated by a blue line on the gums and by stomatitis. In some patients undergoing bismuth therapy systemic symptoms of malaise, nausea, headaches and vague rheumatic muscular and bone pains have been noted. Removal of the bismuth therapy is the principal treatment. Too free local application of bismuth containing powders or too free injection into cavities should be avoided. Large doses of bismuth subnitrate have produced nitrite poisoning by its reduction in the colon.

Most of the bismuth compounds here described (excluding those for use in the treatment of syphilis) belong to the insoluble type. This includes bismuth betanaphtholate, bismuth

bismuth oxy-
septic acid
der on the
romphenate
expected to

have some antiseptic power.

BISMUTH SUBNITRATE — Basic Bismuth Nitrate —

A basic salt which when dried over sulfuric acid for 18 hours yields upon ignition not less than 79 per cent of bismuth oxide (Bi_2O_3). U S P

For description and standards see the U S Pharmacopeia under Bismuth Subnitrate.

PARKE, DAVIS & COMPANY

Bismuth Paste Surgical Bismuth subnitrate 1 part in yellow petrolatum 2 parts

BISMUTH TRIBROMPHENATE — Bismuthi Tribromphenas. — Bismuth Tribromphenol — Xeroform. — A basic bismuth tribromphenate of variable composition.

Actions and Uses. — Bismuth tribromphenate is claimed to be a nonirritant and nontoxic antiseptic. Occasionally cases of sensitization to its local use are noted. It is said to be valuable in ulcers cruris, in impetigo contagiosa and in weeping eczemas; internally, in gastro-intestinal catarrh, proctitis, dysentery, bacillary and choleraic diarrhea, cholera infantum.

Dosage. — From 1 to 3 Gm. per day to adults, from 0.125 to 0.3 Gm. as a dose to children. Externally (as a dusting powder in bandages, etc.) like iodoform in lotions and in ointments in 3 to 10 per cent strength.

Tests and Standards.

Bismuth tribromphenate is an amorphous yellow powder, neutral to moistened litmus paper. It is only slightly soluble in water, alcohol, chloroform, liquid petroleum, or vegetable oils. Alkalies and strong acids decompose it. It is stable at temperatures below 125°C.

Boil about 1 Gm of the salt with 10 cc of sodium hydroxide solution, filter the liquid and acidulate the filtrate with sulfuric acid the white curdy precipitate produced, when washed and dried melts at 200°C. (after distillation)

Free oil the mixture and again filter the latter filtrate leaves not more than 0.005 Gm of residue on evaporation and gentle ignition (alkalis and alkali earths)

Shake 2 Gm of bismuth tribromphenate 20 cc of ether, and 20 cc of mixture of equal volumes of hydrochloric acid and distilled water in a separatory funnel for one or two minutes. Draw off the aqueous portion and concentrate to about 4 cc pour it into 100 cc of distilled water, filter a cloudy water. Mix one portion does not become as of ammonia tint (copper) another portion is not immediately affected by barium nitrate test solution (sulfate)

Heat gently a mixture of about 0.2 Gm of bismuth tribromphenate with 5 cc of potassium hydroxide solution and about 0.2 Gm of aluminum wire the vapors evolved do not turn red litmus blue (nitrates)

Shake 1 Gm of bismuth tribromphenate with 10 cc of distilled water and 10 cc of 15% sodium hydroxide solution

not darken on standing thirty minutes (arsenic)

Mix 0.5 Gm of the salt with 10 cc of a mixture of equal parts of hydrochloric acid and distilled water no effervescence should occur (carbonate)

To about 0.5 Gm of bismuth tribromphenate accurately weighed add 20 cc of hydrochloric acid and digest on a water bath. Add 150 cc of water and filter. Rinse the beaker with 30 cc of acidulated water and allow the washings to run through the filter. Saturate the combined filtrate and washings with hydrogen sulfide (care being exercised that the solution is not too acid so as to prevent quantitative sulfide wash ammonium Allow hydroxide of bismuth - than 55 taken, correct cent of bismuth

SCIHERING & GLATZ, INC.

Xeroform (Powder): 30 Gm and 435 Gm bottles Bismuth tribromphenate

Mercury

Compounds of mercury are used for the preparation of antiseptic and disinfecting solutions. They have a limited germicidal activity for non sporulating bacteria. They cannot be relied upon to kill bacterial spores even after several hours exposure. In recent years solutions of compounds of mercury with dyes or other organic radicals have been used extensively in place of mercuric chloride, mercuric cyanide and mercuric iodide for disinfection of the skin for the treatment of infected wounds and for local treatment of certain bacterial infections. In general these organic compounds of mercury are claimed to be less toxic and less irritating than the older chlorides, iodides and cyanides of mercury. They are highly bacteriostatic and hence may be found to be of distinct value as antiseptics even though their germicidal activity, especially for bacterial spores, has not been conclusively demonstrated. Claims for their ability to penetrate deeply into living tissue and to act as efficient chemotherapeutic agents after injection into the blood stream have not been established. Their antibacterial activity is very greatly diminished in the presence of serum or other proteins.

Inorganic

MERCURIC CYANIDE — Hydrargyri Cyanidum — Hydrargyrum Cyanatum — $\text{Hg}(\text{CN})_2$ — The mercuric salt of hydrocyanic acid

Actions and Uses—Mercuric cyanide has been reported to be as actively antiseptic as mercuric chloride and to be less irritating, but this has been questioned. It is used locally and internally as is mercuric chloride. Blum and Schwab (*Presse Med* 30: 1081 [Dec 16] 1922) highly recommended this drug as a diuretic in cardiac (but not in renal) disease. They give it in doses of 40 to 50 mg by intravenous or intramuscular injection. They state, however, that mercury should be used as a diuretic only as a last resort when other drugs have failed.

Dosage—Internally from 4 to 8 mg locally, solutions of from 1 in 4000 to 1 in 2000 may be used for applications to the eye or mucous membranes, from 15 to 2 cc of a 1 per cent solution may be used hypodermically without causing local irritation. Death has occurred from the use of a vaginal injection containing 0.9 Gm of mercuric cyanide.

In diphtheria and croup it is used in 0.01 per cent solution as a gargle. In fibrinous rhinitis it is used on a tampon in 0.04 per cent solution.

Tests and Standards—

Mercuric cyanide occurs in colorless or white, prismatic crystals or white powder. It has a bitter taste (the salt of mercuric cyanide is soluble in water, alcohol and is very

When slowly heated in a glass tube, the salt decrepitates and decomposes into metallic mercury with a purple flame consisting of paracyanogen dissipated. If 1 part of in a dry test tube it will afterward become red, a shaped crystals. On addition of the salt, the odor of aqueous solution of the should not yield on the gradual addition of a few drops of potassium iodide solution, either a red or a reddish precipitate, soluble in an excess of the precipitant, nor should it yield a white precipitate with silver nitrate solution (*mercuric chloride*). If mercuric cyanide is dissolved in an aqueous solution of sodium chloride, the addition of phenolphthalein to this solution should produce no red coloration (*mercuric oxide*). Ammonia should not color an aqueous solution blue (*mercuric oxide*). Ammonia water dissolves mercuric cyanide without producing a white precipitate (*oxycyanide*).

MALLINGKRODT CHEMICAL WORKS

Mercuric Cyanide (*Powder*): bulk

MERCK & Co, INC

Mercuric Cyanide (*Powder*): bulk

POTASSIUM MERCURIC IODIDE—Potassii Hydrargyri Iodidum.—A complex salt, K_2HgI_4 , formed by the interaction of one molecule of mercuric iodide with two molecules of potassium iodide and containing about 25.5 per cent of mercury.

Actions and Uses—Potassium mercuric iodide is used for the same purposes as mercuric iodide, over which it has some advantages because of its solubility. It is germicidal for many non sporulating bacteria. However, there seems to be no work to show how much the activity is decreased when an excess of potassium iodide is present. In comparison with mercuric chloride it is claimed to have a greater safety factor. Weight for weight, potassium mercuric iodide is about one half as toxic as mercuric chloride according to animal experiments, in proportion to the mercury content, however, potassium mercuric iodide and mercuric chloride possess about the same toxicity.

Externally, potassium mercuric iodide is used for skin disinfection, irrigations and disinfection of instruments and of excreta and discharges.

Dosage—As a disinfectant it is used in concentrations of 1 in 100 to 1 in 10,000. For irrigation of wounds, it is desirable to render the solution isotonic by addition of 0.9 per cent sodium chloride. Solutions of potassium mercuric iodide may be prepared

(1) By dissolving 1 part by weight of mercuric iodide and 1 part by weight of potassium iodide in a small amount of water and then diluting to proper strength, such a solution

will contain about 20 per cent excess of potassium iodide, sufficient to prevent precipitation of mercuric iodide from dilute solutions of the complex salt (1 Gm mercuric iodide is equivalent to 1.7 Gm potassium mercuric iodide)

(2) By dissolving potassium mercuric iodide in water containing potassium iodide. Solutions made from potassium mercuric iodide alone have a tendency to decompose with precipitation of mercuric iodide, hence it is necessary to have present an excess of potassium iodide equivalent to about 20 per cent by weight of the amount of potassium mercuric iodide used

Tests and Standards—

Potassium mercuric iodide occurs as yellow crystals, deliquescent in

ization of mercuric iodide

Treat about 0.2 Gm of potassium mercuric iodide with 1 cc of water and add 1 cc of chloroform and 0.5 cc of ferric chloride solution. The chloroform shows the characteristic color of iodine. Treat about 0.1 Gm of the salt with 2 cc of sodium hydroxide solution and add a few drops of formaldehyde solution. A black precipitate of metallic mercury is produced.

Potassium mercuric iodide loses not more than 4 per cent of its weight when dried at 120°C for four hours.

Transfer about 1.5 Gm of potassium mercuric iodide accurately weighed to a 100 cc volumetric flask and dissolve in 15 cc of water then dilute to 100 cc. Pipette immediately 10 cc of the solution into a glass stoppered 250 cc bottle and add 35 cc of hydrochloric acid and 5 cc of chloroform. Titrate the solution with tenth normal potassium iodate (10.701 Gm in 1000 cc) stoppering the bottle and shaking the contents well after each addition. The addition of the potassium iodate solution is continued until the iodine which was first liberated disappears and the chloroform shows no pink color. The iodine content calculated to the dry salt is not less than 63.4 per cent nor more than 65.5 per cent.

Dissolve about 2.5 Gm of potassium mercuric iodide accurately weighed in about 10 cc of water and add sufficient potassium iodide solution to prevent precipitation of mercuric iodide. Introduce the solution and washings into a cathode cup previously weighed with its metal

gradually increase it will be 2 to rotating the anode minutes wash with ul interrupting the

DAVIS & GECK, INC

Kalmerid Tablets Potassium Mercuric Iodide Each tablet contains potassium mercuric iodide 0.5 Gm potassium iodide 0.37 Gm ammonium chloride 125 mg and eosin "Y" 5 mg

U S patent 1 276 119 (Aug 20 1918 expired) U S trade mark 116 042

PARKE, DAVIS & COMPANY

Discs Potassio-Mercuric Iodide Each disc represents mercuric iodide 97.2 mg potassium iodide 97.2 mg and sodium bicarbonate 2.9 Gm Colored blue

Discs Potassio Mercuric Iodide Each disc represents mercuric iodide 24.3 mg potassium iodide 24.3 mg and sodium bicarbonate 1.04 Gm Colored blue

YELLOW MERCURIC OXIDE—Yellow Precipitate—When dried to constant weight at 110° C contains not less than 99.5 per cent of HgO —U S P

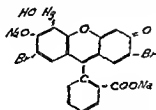
For description and standards see the U S Pharmacopeia under Yellow Mercuric Oxide and Yellow Mercuric Oxide Ointment

MANHATTAN EYE SALVE COMPANY, INC

Yellow Oxide of Mercury, Adrenalin Chloride, and Phenol Ointment—Yellow oxide of mercury, 1 per cent, solution of adrenalin chloride 2 per cent menthol 0.04 per cent phenol, 0.2 per cent anhydrous wool fat 10 per cent and white petrolatum sufficient to make 100 per cent Put up in collapsible tubes for application to the eye

Organic

MERBROMIN—Mercurochrome—The disodium salt of 2,7-dibromo-4-hydroxymercurofluorescein. When dried to constant weight at 110° C and assayed Merbromin yields not less than 24 per cent and not more than 26.7 per cent of Hg and not less than 18 per cent and not more than 21.3 per cent of Br —N I



For description and standards see the National Formulary under Merbromin Solution of Merbromin and Surgical Solution of Merbromin

Actions and Uses—Merbromin is a nonirritating moderately active antiseptic. When applied to the skin mucous membranes and wounds it exerts bacteriostatic and bactericidal action. The 2 per cent aqueous solution of merbromin acts more slowly than tincture of iodine-U S P, but has more prolonged bacteriostatic effect. The aqueous alcohol acetone solution called surgical solution of merbromin is more rapid in its action than the aqueous solution and may be used for preoperative skin disinfection. Merbromin penetrates significantly only into dying or dead tissue.

The drug is tolerated in a strength of 1 per cent by the bladder, renal pelvis and urethra, a 2 per cent solution applied to the anterior urethra causes only temporary discomfort. When tested by intravenous injection into rabbits the danger point is reached with a dosage of 25 mg per Kg, and 5 mg causes a decrease in phenolsulfonphthalein excretion and an albuminuria which lasts about a week. Dogs are more resistant. No systemic effects have been observed following its local application in the human. Merbromin has been used in cystitis and urethritis, also in affections of the eye and affections of the ear, such as otitis media. Although merbromin has been used intravenously the Council does not recognize the use of the drug for this purpose. The intravenous injection may be followed by severe toxic symptoms.

Dosage—In the treatment of infections of the kidney pelvis the ureters are catheterized and the pelvis gently filled with a 1 per cent solution, the catheter is plugged and the solution retained for five minutes. In the treatment of bladder conditions, 25 to 30 cc. of the 1 per cent solution is introduced into the bladder and retained for one hour or longer the treatment being given daily or on alternate days, or at longer intervals according to circumstances. In anterior gonococcus urethritis, the anterior urethra is filled with a 1 per cent solution and the solution retained for five minutes. If the posterior urethra be involved, the solution is gently retained for an hour or more. In rare cases considerable irritation is produced particularly in those with residual urine. Later, in the treatment of acute anterior gonorrhea, a 2 per cent solution is used every three hours. Solutions are self sterilizing and should not be boiled. They should be made up from the drug itself as the tablets are not suitable for this purpose.

Merbromin is incompatible with acids with the salts of most alkaloids and with most local anesthetics. The aqueous solution stains the skin red but the discoloration may be removed by washing in a solution of sodium hypochloride (solution of chlorinated soda).

HYNSON, WISTCOTT & DUNNING, INC

Mercurochrome (Powder): bulk

U. S. patent 1 535 003 (April 11, 1925, expired), U. S. trade mark 197,189

Mercurochrome, 2 per cent Aqueous Solution

Surgical Solution of Mercurochrome Merbromin, 2 per cent dissolved in a vehicle consisting of 55 parts of 95 per cent alcohol, 10 parts of acetone, and 35 parts of water, to which has been added sodium carbonate, 0.1 per cent

Tablets Mercurochrome 0.3 Gm

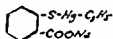
PREMO PHARMACEUTICAL LABORATORIES, INC

Merbromin Crystals 10 Gm 100 Gm 500 Gm and 1 000 Gm bottles

Solution of Merbromin—N F 75 cc 15 cc 30 cc 473 cc and 3 785 cc bottles

Surgical Solution of Merbromin—N F 473 cc and 3 785 cc bottles

MERTHIOLATE—Merthiolate Sodium—Sodium ethyl mercuri thiosalicylate— $C_6H_4HgSC_6H_4COONa$ Merthiolate contains from 49.15 to 49.65 per cent of mercury in organic combination



Actions and Uses—Merthiolate is germicidal for many non sporulating, usual laboratory tests and disinfecting tissue surfaces at this agent, like other organic compounds cannot be guaranteed to kill when spor forming organisms are present. Merthiolate is much less toxic than mercuric chloride.

• Merthiolate 1 in 10 000 may be useful as a preservative of biologicals of not too high protein content. This concentration however, does not necessarily prevent growth of micro organisms in stored, liquid plasma.

Dosage—For disinfection of instruments 1 in 1 000 aqueous solution, for application to the intact skin tincture 1 in 1 000, for application in wounds and to denuded surfaces, aqueous solution 1 in 1 in 10 000 nasal mucous membranes, for irrigations, 1 for urethral

Tests and Standards—

Recrystallize this
um over sulfuric
into a 1 per cent
which is soluble in
trate solution to a
te separates. Add
solution of merthi
s of copper sulfate
a green precipitate

separates
Shake 0.3 Gm. of merthiolate accurately weighed with 20 cc. of anhydrous ether for ten minutes, filter, evaporate the ether and dry in a vacuum over sulfuric acid to constant weight. The weight of the residue does not exceed 0.003 Gm. Dissolve about 0.2 Gm. of merthiolate in 5 cc. of sulfuric acid; not more than a slight yellow color is produced. Mix equal parts of a 1 per cent solution of merthiolate and of ammonium sulfide; a white precipitate is formed but no blackening occurs after standing forty-eight hours. Dry 0.1 Gm. of merthiolate to constant weight in a vacuum over sulfuric acid; it does not lose more than 0.5 per cent in weight.

Transfer to a 0.2 Gm. of merthiolate accurately weighed to a 100
lone acid
romine no
y saturate
crucible
ether dry
spends to
calculated
to the dried substance

ALLEN LABORATORIES, INC.

Medipax Brand of Vaginal Tampon-Suppositories with Merthiolate 1:2,000: The suppository contains 2.25 mg of merthiolate in 4.5 Gm of glycerogelatin shaped for insertion.

Actions and Uses—A product devised to enable prolonged medication to the upper vaginal vault and cervical region by incorporating a merthiolate medicated suppository together with a tampon on a single applicator. After insertion into the vagina the suppository melts at body temperature. The tampon which is contained in the applicator and is composed of surgical cotton $1\frac{1}{4}$ inches wide by $2\frac{3}{4}$ inches long is released by appropriate pressure on the sleeve of the applicator. The tampon swells by taking up moisture thus holding the medication in contact with the desired parts. A cord is attached to the tampon for convenient removal.

ELI LILLY AND COMPANY

Merthiolate Jelly 1:1,000 Merthiolate 0.1 per cent, eucalyptol 0.016 per cent and eugenol 0.016 per cent in a water soluble base.

Merthiolate Ointment 1:2,000 Merthiolate 0.05 per cent in a petrolatum base.

Merthiolate Ophthalmic Ointment, 1 5,000 Contains merthiolate 1 part in 5 000 parts of a base consisting of liquid petrolatum and wool fat with small amounts of paraffin white petrolatum and ceresin

Merthiolate Solution 1 1,000 One gram of merthiolate and 1 Gm of monoethanolamine in 1 000 cc of water buffered with 1 4 Gm of sodium borate and containing sodium chloride to make the solution approximately isotonic

Merthiolate Suppositories 1 1,000 Each suppository weighs approximately 10 Gm and contains merthiolate 1 1 000 in a glycerin and gelatin base consisting of 17 3 parts glycerin and 7 6 parts gelatin

Tincture Merthiolate 1 1 000 Contains merthiolate 0 1 Gm and monoethanolamine 0 1 Gm dissolved in alcohol 50 cc, acetone 10 cc. and water, sufficient to make 100 cc.

U S Patent 1 672 613 (June 5 1928 exp red) U S trademark 252 187

METAPHEN—The anhydride of 4 nitro 3 hydroxy mercuri ortho cresol $C_6H_3CH_3O NO_2 Hg$ When metaphen is dissolved in alkali solution the anhydride ring opens forming the resulting sodium derivative Metaphen contains from 56 to 57 per cent of mercury in organic combination It is used only in form of the sodium salt



Actions and Uses—Metaphen is claimed to be more germicidal than mercuric chloride when tested on cultures of *Staphylococcus aureus* and *Eberthella typhosa* It is stated to be relatively nonirritating when applied to mucous membranes or the skin and to be without deleterious action on metallic instruments or rubber Metaphen is claimed to be relatively non toxic

Metaphen is proposed for use in the treatment of gonorrhea and infections of the eye for the disinfection of skin surgical instruments and rubber if no sporulating pathogenic organisms are present

Dosage—Solutions of metaphen in water are prepared with the aid of sodium hydroxide For disinfection of instruments solutions of 1 in 5 000 to 1 in 1 000 for application to the

skin solutions of 1 in 5,000 and 1 in 1,000, for ophthalmological and for urethral irrigation solutions of 1 in 5,000 to 1 in 10,000 are proposed

Tests and Standards—

Metaphen is a yellow, odorless and tasteless substance, insoluble in water, almost insoluble in methyl alcohol, acetone, ether and aqueous sodium carbonate and sodium bicarbonate solution, soluble in dilute aqueous sodium hydroxide solution and in ammonium hydroxide solution, soluble in boiling glacial acetic acid and in nitric acid at room temperature

Suspend 0.1 Gm of metaphen in 10 cc of glacial acetic acid allow to stand for five minutes decant and wash the residue three times by decantation with distilled water, repeat the procedure three times, then dissolve the residue in 15 cc of distilled water and 1 cc of 50 per cent sodium hydroxide solution add 0.5 Gm of sodium hydrosulfite and heat to boiling a heavy deposit of metallic mercury is obtained (combined mercury) Add 50 cc of benzene to 0.5 Gm of metaphen shake for two minutes filter, and evaporate the filtrate to dryness the residue does not weigh more than 0.005 Gm (absence of uncombined 4-nitro-2-cresol) Dissolve 0.4 Gm of metaphen in 3 cc of 15 per cent sodium hydroxide solution and 30 cc of water, divide into two equal portions and transfer to two test tubes to one add 0.1 Gm of sodium hydrosulfite, allow to stand for one hour, filter and compare the filtrate with the other tube the first tube is no darker than the control (absence of dinitrocresol) Treat 0.1 Gm of metaphen with 20 cc of 1 per cent sodium hydroxide solution no insoluble residue remains (absence of inorganic mercury salts or mercury derivative of nitroindazole)

Transfer about 0.2 Gm of metaphen, accurately weighed to a dry Erlenmeyer flask, add 2 Gm of potassium permanganate mix well and then add 5 cc of diluted sulfuric acid allow the solution to stand for 15 minutes, then carefully add 15 cc of sulfuric acid (concentrated) in 2 cc portions, and allow the mixture to stand for another 10 minutes Decolorize the mixture drop by drop with hydrogen peroxide solution, after decolorization add 5 cc of water and boil for from five to eight minutes Cool add 15 cc of water and saturate the solution with hydrogen sulfide keep the solution saturated for 18 hours Transfer the precipitated mercuric sulfide to a Gooch crucible, wash with hydrogen sulfide water, then with hydrogen sulfide water acidified with sulfuric acid wash thoroughly with distilled water then with alcohol and carbon disulfide The carbon disulfide should remain over the precipitate for approximately one-half hour Wash finally with acetone Dry in an oven for one-half hour at 100 to 110 C and weigh the mercuric sulfide the amount of mercury calculated from the weight of the mercuric sulfide is not less than 56 per cent, nor more than 57 per cent in the dried substance

ABBOTT LABORATORIES

Metaphen Ophthalmic Ointment: Metaphen 1 3,000 in an ointment base containing anhydrous wool fat, 25 per cent, and petrolatum 75 per cent

Solution Metaphen, 1-500. Metaphen dissolved in water by means of sodium hydroxide to form the sodium salt of metaphen

Solution Metaphen, 1-2,500. Metaphen dissolved in water containing 0.33 per cent each of sodium bicarbonate and sodium carbonate to form the sodium salt of metaphen

Tincture Metaphen, 1:200: Metaphen, 0.5 Gm, dissolved in a mixture of acetone, 10 cc, water, 40 cc and alcohol, 50 cc

U S patent reissue 17,563 (Sept. 22, 1925, expired) U S trademark 205,507

ALLEN LABORATORIES, INC.

Medipax Brand of Vaginal Tampon-Suppositories with Metaphen, 1:2,000. The suppository contains 2.25 mg of metaphen in 45 Gm of glycerogelatin, shaped for insertion.

Action and Uses—A product devised to enable prolonged medication to the upper vaginal vault and cervical region by incorporating a metaphen medicated suppository together with a tampon on a single applicator. After insertion into the vagina the suppository melts at body temperature. The tampon which is contained in the applicator and is composed of surgical cotton $1\frac{3}{4}$ inches wide by $2\frac{3}{4}$ inches long is released by appropriate pressure on the sleeve of the applicator. The tampon swells by taking up moisture, thus holding the medication in contact with the desired parts. A cord is attached to the tampon for convenient removal.

Phenylmercuric Compounds

Phenylmercuric chloride and basic phenylmercuric nitrate were the first of the organic mercurial compounds of their type found to possess effective bacteriostatic and bactericidal activity against certain pathogenic micro organisms. Evidence to indicate that other phenylmercuric salts are similarly effective suggests that the activity of such compounds is primarily attributable to the phenylmercuric ion. In general, phenylmercuric salts are highly dissociable in solutions to provide phenylmercuric ions effective concentrations of which are dependent on the widely varying solubility of the salts employed. In acid, neutral or slightly alkaline solutions, chlorides, bromides, iodides and soaps react with phenylmercuric ion to precipitate a phenylmercuric salt. Phenylmercuric chloride is soluble only to the extent of 1 part in 20,000 of water, the bromide is still less soluble and the iodide is quite insoluble. For this reason the chloride has been supplanted by the more soluble basic phenylmercuric nitrate and other salts.

The phenylmercuric radical (C_6H_5Hg)⁺ is more stable in acid than in alkaline solutions of its salts. Aqueous solutions containing phenylmercuric ions buffered with inorganic or organic acids are fairly stable. In the presence of organic solvents the stability is lowered but is still relatively good. Because of the fact that buffered solutions of phenylmercuric salts are more stable and also less irritating to tissue than unbuffered solutions, the former are preferable for pharmaceutical purposes. In general the buffered solutions are stainless, colorless, odorless without action on rubber and are noncorrosive to the common metals other than aluminum except as these properties may be influenced by the particular acid employed. Solutions of phenyl

mercuric salts may determine increasing amounts of mercuric and mercurous ions or free mercury as the result of gradual decomposition of phenylmercuric ions.

There is evidence to indicate that phenylmercuric compounds are of comparatively high germicidal and inhibitory value against a variety of pathogenic bacteria and of relatively low toxicity to human tissue. As with the other types of organic mercurial antiseptics, however, they cannot be depended on to kill bacterial spores even after several hours exposure. The presence of buffered solutions of phenylmercuric salts does not interfere with the precipitating reaction of human serum; the action of compounds, the digestive action of pepsin and trypsin or the antigenic power of vaccine. Despite their relatively low toxicity, phenylmercuric compounds may produce irritation, "burns" or poisoning in occasional individuals with undue sensitivity. The minimum lethal intravenous dose for rabbits of a 0.062 per cent (1:1500) aqueous solution of basic phenylmercuric borate (buffered with 0.1 per cent boric acid) is 7 cc. per kilogram of body weight. Other evidence indicates that the minimum lethal oral dose for these animals is approximately three times the intravenous dose. The toxicity of solutions of this and other phenylmercuric salts may be expected to vary according to the concentration of phenylmercuric ions, the presence of organic solvents, the acid which is added as a buffer to render them stable and the degree of decomposition. The appearance of metallic mercury as a precipitate in solutions of phenylmercuric salts indicates extensive decomposition.

MEPPHENYL BORATE TINCTURE 1:500—Tincture of Phenylmercuric Borate 1:500—A tincture consisting of acetone 4.6 per cent, alcohol 43.2 per cent and water 50 per cent, containing phenylmercuric borate 0.2 per cent, with 1.0 per cent each of boric acid and sodium acid phosphate. Phenylmercuric borate can be considered to have the formula $C_6H_5HgBO_3 \cdot H_2O$, although a product of this composition may be difficult to isolate. Solutions which can be considered to contain phenylmercuric borate may be prepared by the addition of boric acid in appropriate amounts to solutions of phenylmercuric hydroxide.

Actions and Uses—Meryphenyl borate is recognized for use in tincture form for external use as an antiseptic for the prophylactic and therapeutic disinfection of the skin, superficial injuries and wounds. Buffered solutions of this compound are claimed to be somewhat less irritating than certain other phenylmercuric compounds.

Dosage—For prophylactic preoperative preparation of the intact skin, disinfection of recent soft tissue injuries and the treatment of superficial wounds a 1:500 tincture of phenylmercuric borate may be applied full strength, for application to mucous membranes, in wet dressings or continuous irrigation

Actions and Uses—Merphenyl nitrate (basic) is recognized for external use in solution or ointment as an antiseptic for the prophylactic and therapeutic disinfection of the skin superficial abrasions, lacerations, wounds and infections.

Dosage—For prophylactic disinfection of the intact skin and minor lesions the 1:1,500 aqueous buffered solutions may be applied full strength; for application to mucous membranes or for the application of wet dressings or continuous irrigation to wounds, a 1:1,000 solution is recommended. The 1:1,000 solution (prepared by) is applied ten to fifteen times daily as a dressing, the being too concealing by the addition of about 0.5 per cent of sodium chloride. Approximately $\frac{3}{4}$ teaspoon of noniodized table salt to each pint of diluted solution is recommended. This amount of sodium chloride does not produce excessive precipitation. The full strength (1:1,500) solution should never be used to wet bandages or dressings. The 1:1,500 oxycholesterin base ointment may also be employed for the prophylactic disinfection of minor injuries or may be applied twice daily for the treatment of superficial infections.

Tests and Standards—

Basic phenylmercuric nitrate is an odorless white crystalline powder, which melts with decomposition between 175 and 185 C. (extremely pure specimens melt as high as 192 C.) It is soluble (1:200) in glycerin, slightly soluble (1:600) in alcohol and very slightly soluble (1:1,200) in water. Its apparent solubility in water is increased if nitric acid or alkalis are present. Aqueous solutions of basic phenylmercuric nitrate are incompatible with halides, which cause the precipitation of the nearly insoluble halide compounds e. g. phenylmercuric chloride ($\text{C}_6\text{H}_5\text{HgCl}$). The pH of a 0.1 per cent aqueous solution of basic phenylmercuric nitrate is approximately 3.7.

Add 3 cc. of sulfuric acid to about 0.1 Gm. of basic phenylmercuric nitrate; the mixture becomes yellow and the odor of nitrobenzene is evolved. Add 1 cc. of diluted hydrochloric acid to 5 cc. of saturated aqueous solution of basic phenylmercuric nitrate; a white precipitate forms. Filter, wash the precipitate with cold water, dry it on a porous plate; the melting point of the product is between 248 and 255 C. Solutions of basic phenylmercuric nitrate respond to the U. S. P. test for nitrate. Add 5 cc. of ammonium sulfide solution to 5 cc. of a saturated solution of basic phenylmercuric nitrate; there is no reaction in the cold; heat the mixture for ten minutes in a boiling water bath; a black precipitate forms.

Add 5 cc. of sodium hydroxide solution to 5 cc. of a saturated solution of basic phenylmercuric nitrate; a yellow precipitate forms (absence of mercuric ions); the solution does not blacken (absence of mercurous ions). Dissolve 0.1 Gm. of basic phenylmercuric nitrate in 10 cc. of water; the solution is clear and colorless.

nitrate the
hed portion of
method the
re than 63.50

per cent.

Determine the nitrogen content of an accurately weighed portion of basic phenylmercuric nitrate by the micro Dumas method or by the method described in the fifth edition of *Methods of Analysis* of the

Association of Official Agricultural Chemists, page 27, section 27 the nitrogen content is not less than 205 per cent nor more than 225 per cent

Determine the phenylmercuric ion content of 0.2 Gm of basic 10 cc of water and acidified with titrate the solution with twentieth 2 cc of saturated ferric ammonium thiocyanate or Compare the color produced cc of the ammonium thiocyanate twentieth normal ammonium thiocyanate Gm of phenylmercuric ion the phenylmercuric ion content found is not less than 87.0 nor more than 87.9 per cent

HAMILTON LABORATORIES, INC.

Merphenyl Nitrate (Basic) Solution, 1:1,500: An aqueous solution of basic phenylmercuric nitrate 0.067 per cent with boric acid 0.1 per cent

Merphenyl Nitrate (Basic) Ointment, 1:1,500: A water-in-oil emulsion ($\frac{3}{4}$ aqueous, $\frac{1}{4}$ oil phase) of an oxycholesterin base containing basic phenylmercuric nitrate 0.067 per cent with boric acid 0.1 per cent

U. S. trademark 318,039

MERPHENYL PICRATE TINCTURE 1:200 WITH PICRIC ACID—Tincture of Phenylmercuric Picrate 1:200 with Picric Acid 12%—A tincture consisting of acetone 10 per cent, alcohol 50 per cent and water 38.3 per cent, containing phenylmercuric picrate 0.5 per cent with picric acid (trinitrophenol) 12 per cent. Phenylmercuric picrate can be considered to have the formula $C_6H_5HgOC_6H_2(NO_2)_3$, although a product of this composition may be difficult to isolate. Solutions which can be considered to contain phenylmercuric picrate may be prepared by the addition of picric acid (trinitrophenol) in appropriate amounts to solutions of phenylmercuric hydroxide.

Actions and Uses—Merphenyl picrate, in an acetone alcohol tincture with picric acid is primarily intended as a prophylactic disinfectant in the preoperative preparation of the intact skin and for recent abrasions, lacerations and wounds. It may also be employed in the treatment of superficial infections, particularly when the drying effect of acetone and alcohol is desired. Owing to its staining quality the picrate compound is useful to delineate the field or area of application. Picric acid is added in sufficient concentration to provide fair stability, but the amount present is also sufficient to exert some disinfectant action in itself. Because of its high toxicity internally the possibility of poisoning due to absorption of picric acid from applications of the tincture to large denuded areas of the skin or to mucous membranes should be kept in mind.

Dosage—For prophylactic preoperative skin preparation, disinfection of soft tissue injuries and the treatment of superficial infections tincture of phenylmercuric picrate 1:200 with picric

acid 1.2 per cent is applied full strength, in wet dressings or continuous irrigation for infected wounds, a concentration of phenylmercuric picrate not greater than 1 15,000 should be used (prepared by diluting the 1 200 tincture approximately seventy five times with water). When used as a wet dressing, undue concentration of the diluted solution from unavoidable evaporation should be prevented by the addition of about 0.5 per cent of sodium chloride.
table salt to each
amount of sodium
tation The full s
to wet dressings or bandages

Tests and Standards —

Merphenyl picrate tincture 1 200 with picric acid is a strongly yellow colored solution which possesses the odor of acetone and alcohol and a μ m value of about 20. Its specific gravity is between 0.8980 and 0.901 at 25 C.

To 2 cc of merphenyl picrate tincture 1 200 add 2 cc of water and 2 drops of 1 per cent sodium chloride solution a white precipitate, which is soluble in sodium hydroxide and may be reprecipitated by the addition of nitric acid is formed. To 10 cc of merphenyl picrate tincture 1 200 add 2 cc of saturated sodium chloride solution a precipitate forms filter wash the precipitate with cold water, dry on a porous plate the melting point of the product is between 245 and 255 C.

To 5 cc of merphenyl picrate tincture 1 200 add 5 cc of water and 2 cc. of diluted nitric acid, extract the solution with three 10 cc portions of ether combine the ether extracts filter through a cotton pledget and evaporate the ether yellow crystals are obtained which melt at from 120 to 123 C.

To 2 cc of merphenyl picrate tincture 1 200 add 2 cc of water followed by 2 cc of potassium iodide solution added a drop at a time a white precipitate forms in the yellow solution that at no time shows traces of orange or red color and is insoluble in the excess of potassium iodide (*mercuric ions*). To 2 cc of merphenyl picrate tincture 1 200 add an excess of sodium hydroxide solution the solution becomes orange-red but there is no precipitate and the solution does not blacken (*mercurous salts*). To 3 cc of merphenyl picrate tincture 1 200 add 5 cc of sulfuric acid cool overlay with a saturated solution of ferrous sulfate a brown ring does not appear (*nitrate*).

The mercury content of merphenyl picrate tincture 1 200 can be determined by a suitable electrolytic method the mercury content is equivalent to not less than 0.26 per cent nor more than 0.28 per cent of merphenyl ion. The merphenyl ion content also may be determined, as directed under merphenyl borate tincture 1 500, after removal by ether extraction of the picric acid from an acidified portion of the tincture (nitric acid).

Caution Merphenyl picrate tincture 1 200 with picric acid is more liable to decomposition on aging than certain other phenylmercuric salts.

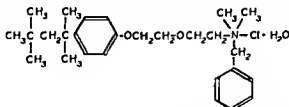
HAMILTON LABORATORIES, INC

Merphenyl Picrate Tincture 1 200 with Picric Acid
bulk.

U S trademark 318 039

Quaternary Ammonium Compounds

PHEMEROL CHLORIDE — [p-(2-methyl-4,4-dimethyl pentano 2) (phenoxy-ethoxy-ethyl)] dimethyl benzyl ammonium chloride monohydrate — $C_{27}H_{45}O_2$, $NCl \cdot H_2O$ M W 466.09. Phemerol chloride has the following structural formula



Actions and Uses — Finetured Phemerol Chloride 1:500 and Solution Phemerol Chloride 1:1,000 (aqueous) are proposed as general purpose germicides and antiseptics.

Dosage — Both the tincture and the solution are used full strength except in the nose and eye. For use in the nose and eye only the solution should be used, diluted with four parts of water.

Tests and Standards —

Phemerol chloride appears as colorless odorless crystals possessing a very bitter taste. It may be recrystallized from a chloroform solution by the addition of ether, in the form of very thin plates which may assume a hexagonal shape. These crystals possess a high birefringence parallel extinction and positive elongation and are biaxial with refractive indexes of 1.580 and 1.560. These crystals and the original material sink slightly on the hot stage at 120°C and melt at 164-166°C. The pH of a 1 per cent solution of phemerol chloride is between 4.8 and 5.5.

Mineral acids and many salt solutions precipitate phemerol chloride from solution more concentrated than 2 per cent as an oil which crystallizes on drying and has the same properties as phemerol chloride. A solution of phemerol chloride yields a flocculent white precipitate with soap solutions. To 1 cc of a 1 per cent solution of phemerol chloride add 2 cc of ethanol, 0.3 cc of dilute nitric acid and 1 cc of silver nitrate solution; a flocculent white precipitate appears which is insoluble in dilute nitric acid but soluble in dilute ammonia water.

Dissolve 0.1 Gm of phemerol chloride in 1 cc of sulfuric acid and add three minutes later zinc and nitrate to 1 cc. G salt (sodium xide the solu-

tion turns orange-red and a brown precipitate may appear.

Transfer approximately 1 Gm of phemerol chloride accurately weighed to a tared platinum dish and dry in an oven at 100°C to constant weight; the loss in weight is not less than 3.5 nor more than 4.2 per cent. Ignite the residue; the weight of ash is not more than 0.1 per cent.

merol chloride accurately
of water add 10 cc of
nitrate dilute to the mark
25 cc of the filtrate add
te and titrate with tenth
content is not less than 7.6
dried substance

Transfer an accurately weighed sample of phemerol chloride to a kjeldahl flask and digest with sulfuric acid in the presence of selenium cool, dilute with water make alkaline with sodium hydroxide distill the ammonia into the standard acid solution and titrate the excess acid the nitrogen content is not less than 2.6 nor more than 3.1 per cent

Dissolve approximately 1 Gm of phemerol chloride accurately weighed in distilled water to make 100 cc of solution Transfer

exactly 25 cc of this solution to a 250 cc flask A
of buffer solution (26% of acetic acid mixed
cent acetic acid mixed
50 cc. of 0.01 molar p
of potassium ferricyan
dissolve in distilled w
distilled water, mix w
shaking Filter throug
first 20 cc of filtrate
to a 250 cc flask A
diluted hydrochloric ac
zinc sulfate solution and titrate with 0.01 normal sodium thiosulfate
using starch solution as the indicator near the endpoint Conduct a
blank determination at the same time with the same quantities of
reagents as the above
thiosulfate
in volum
determin
the aliqu
is not less

PANKE, DAVIS & COMPANY

Tincture Phemerol Chloride 1 500 and Solution
Phemerol Chloride 1 1,000 30 cc 120 cc 480 cc and
3840 cc bottles

U S Patent 2 115 250 (expires April 26 1955) U S trademark
305 545

Zephrine Chloride —(See page 113)

Silver

Silver compounds are used in medicine to secure caustic astringent and antiseptic effects These results are produced by the free silver ions When caustic effects are desired silver nitrate is preferred because the colloidal compounds of silver are largely or completely lacking in caustic properties As an astringent also, silver nitrate is the compound of choice but it must be used in weaker solutions, silver picrate acts similarly The antiseptic action of silver nitrate is complicated by irritation, pain astringency and corrosion These may be desirable for the destruction of tissue or the stimulation of indolent wounds, but when they are not necessary for such purposes they may be avoided by the use of colloidal silver preparations

Caution The long continued use of any silver preparation may produce irremediable discoloration of the skin or mucous membrane (argyria)

Colloidal Silver Preparations

In these the silver does not exist to any great extent as free ions therefore it does not precipitate chlorides or proteins and is noncorrosive and relatively or quite nonastringent

and nonirritant but a considerable degree of antiseptic action is retained. This is not proportional to the total silver content and varies for the different compounds, suggesting that the antiseptic action is due to the liberation of very low concentrations of silver ions which vary for the different compounds.

The mechanism of these effects is analogous to the late action of silver nitrate. This takes place in two stages: (1) the immediate irritant and germicidal effects produced by the direct application of the free silver ions and (2) the later milder antiseptic effects produced by the resolution of the protein silver compounds that were formed in the first stage. If the second stage alone is desired (i. e. mild antiseptics without irritation) the direct application of the colloid compounds may have advantages over their indirect production from silver nitrate, aside from the avoidance of irritation, for the absence of any coagulation membrane facilitates their access to the cells; they form more concentrated solutions than are likely to be formed from the resolution of the silver precipitates *in situ*; the colloidal aggregates may be smaller and therefore more reactive; and because of the absence of irritation they are likely to be more frequently applied and would for that reason secure a more continuous action.

The colloidal silver preparations appear to be quite efficacious for the prophylaxis against gonorrheal infection, evidently killing these organisms on direct contact. Culver (*J Lab & Clin Med* 3:487 [May] 1918) reports that gonococci in hydrocele broth cultures are killed by momentary exposure to 0.5 per cent mild protein silver or to 0.25 per cent strong protein silver. As regards other organisms discordant results have been reported.

Metallic silver and insoluble compounds of silver such as the oxide, the halogen salts (iodide, chloride, etc.) and protein silver precipitates may be brought into colloidal solution, i. e. if they are sufficiently finely divided they become miscible with water so that they apparently go into solution (such colloidal solutions are strictly permanent suspensions of the insoluble substance in a state of ultramicroscopic particles).

The commercial preparations are for the most part produced by dissolving reduced silver or silver oxide or some protein silver precipitate in an excess of a denatured protein and drying *in vacuo*. This results in substances that dissolve very freely although somewhat slowly in water, yielding brown colloidal solutions which contain so little of free silver ions that they do not readily precipitate chlorides or proteins. They consist of indefinite mixtures of metallic silver, silver oxide, and various silver protein compounds, all in colloidal form. The proportions of these and the properties of the mixture vary according to the conditions under which they are produced.

Although there are many gradations, most of the products on the market fall into a small number of fairly definite therapeutic groups

- (A) Protein Silver, Strong Type
- (B) Protein Silver, Mild Type
- (C) Collargol Type
- (D) Electric Type
- (E) Silver Halides

A Protein Silver, Strong Type—Strong protein silver compounds contain the lowest percentage of silver (from 7.5 to 85 per cent), but have the strongest germicidal action and are distinctly irritant. They are therefore, therapeutically intermediate between silver nitrate and mild protein silver. Protargol belongs to this group.

Protargol is said to be prepared by precipitating a 'peptone (albumose) solution with silver nitrate, or with moist silver oxide, dissolving the silver peptonate in an excess of protalbumose, and drying *in vacuo* (Fraenkel)

B Protein Silver, Mild Type—These compounds contain from 19 to 25 per cent of silver and are less irritant. The following belong to this group: Argyn, Cargentos, Solargol, and Solargentum Squibb. Argyn is defined as a colloidal solution of serum albumin. Solargentum Squibb is prepared from alkali gelatin used as a solvent for silver oxide. The solution is then concentrated and dried *in vacuo*. Cargentos is prepared by suspending moist silver oxide in a solution of casein, and heating the mixture until no precipitate is obtained on the addition of solution of sodium chloride and by evaporating the mixture to dryness in an air oven.

C Collargol Type—This contains a much higher percentage (78) of silver said to be in the form of metallic silver, reduced to the colloidal form by chemical means and "stabilized" by a small percentage of egg albumin with products of oxidation. However, the albumin is denatured since it does not precipitate on boiling, and it presumably constitutes the greater part of the 22 per cent that is not silver. Collargol therefore, differs from the preceding class in degree rather than in principle, containing a larger proportion of silver in the form of colloidal metal and oxide, and a smaller proportion in the form of proteinate.

D Electric Type—Metallic silver may be brought into colloidal solution electrically, i. e. by forming an arc between silver electrodes under water. These solutions are very dilute and are not sufficiently stable for concentration. They are also likely to contain silver oxide and sometimes ionized silver.

E Silver Halides—These are mixtures of the colloidal silver salts (ten per cent of silver chloride in Lunosol, 18 to 22 per

and nonirritant but a considerable degree of antiseptic action is retained. This is not proportional to the total silver content and varies for the different compounds, suggesting that the antiseptic action is due to the liberation of very low concentrations of silver ions which vary for the different compounds.

The mechanism of these effects is analogous to the late action of silver nitrate. This takes place in two stages: (1) the immediate irritant and germicidal effects produced by the direct application of the free silver ions, and (2) the later milder antiseptic effects produced by the resolution of the protein silver compounds that were formed in the first stage. If the second stage alone is desired (i.e. mild antiseptics without irritation) the direct application of the colloid compounds may have advantages over their indirect production from silver nitrate, aside from the avoidance of irritation, for the absence of any coagulation membrane facilitates their access to the cells; they form more concentrated solutions than are likely to be formed from the resolution of the silver precipitates *in situ*, the colloidal aggregates may be smaller and therefore more reactive, and because of the absence of irritation they are likely to be more frequently applied and would for that reason secure a more continuous action.

The colloidal silver preparations appear to be quite efficacious for the prophylaxis against gonorrhoeal infection, evidently killing these organisms on direct contact. Culver (*J Lab & Clin Med* 3:487 [May] 1918) reports that gonococci in hydrocele broth cultures are killed by momentary exposure to 0.5 per cent mild protein silver or to 0.25 per cent strong protein silver. As regards other organisms discordant results have been reported.

Metallic silver and insoluble compounds of silver such as the oxide, the halogen salts (iodide, chloride, etc.) and protein silver precipitates may be brought into colloidal solution, i.e. if they are sufficiently finely divided they become miscible with water, so that they apparently go into solution (such colloidal solutions are strictly permanent suspensions of the insoluble substance in a state of ultramicroscopic particles).

The commercial preparations are for the most part produced by dissolving reduced silver or silver oxide or some protein silver precipitate in an excess of a denatured protein and drying *in vacuo*. This results in substances that dissolve very freely although somewhat slowly in water, yielding brown 'colloidal solutions' which contain so little of free silver ions that they do not readily precipitate chlorides or proteins. They consist of indefinite mixtures of metallic silver, silver oxide and various silver protein compounds, all in colloidal form. The proportions of these and the properties of the mixture vary according to the conditions under which they are produced.

Although there are many gradations, most of the products on the market fall into a small number of fairly definite therapeutic groups

- (A) Protein Silver, Strong Type
- (B) Protein Silver, Mild Type
- (C) Collargol Type
- (D) Electric Type
- (E) Silver Halides

A Protein Silver, Strong Type—Strong protein silver compounds contain the lowest percentage of silver (from 75 to 85 per cent), but have the strongest germicidal action and are distinctly irritant. They are, therefore, therapeutically intermediate between silver nitrate and mild protein silver. Protargol belongs to this group.

Protargol is said to be prepared by precipitating a "peptone" (albumose) solution with silver nitrate, or with moist silver oxide, dissolving the silver peptonate in an excess of protalbumose; and drying *in vacuo* (Fraenkel).

B Protein Silver—This group contains from 19 to 75 per cent of silver. It is less irritant. The following are included in this group: a. **Argyn** is defined as a mixture of serum albumin and silver nitrate, used as a solution. It is then concentrated and dried *in vacuo*. **Cargentos** is prepared by suspending moist silver oxide in a solution of casein, and heating the mixture until no precipitate is obtained on the addition of solution of sodium chloride, and by evaporating the mixture to dryness in an air oven.

C Collargol Type—This contains a much higher percentage (78) of silver, said to be in the form of metallic silver reduced to the colloidal form by chemical means and "stabilized" by "a small percentage of egg albumin with products of oxidation. However, the albumin is denatured, since it does not precipitate on boiling, and it presumably constitutes the greater part of the 22 per cent that is not silver. Collargol, therefore, differs from the preceding class in degree rather than in principle, containing a larger proportion of silver in the form of colloidal metal and oxide, and a smaller proportion in the form of proteinate.

D Electric Type—Metallic silver may be brought into colloidal solution electrically, i. e. by forming an arc between silver electrodes under water. These solutions are very dilute and are not sufficiently stable for concentration. They are also likely to contain silver oxide, and sometimes ionized silver.

E. Silver Halides—These are mixtures of the colloidal silver salts (ten per cent of silver chloride in Linosol, 18 to 22 per

cent of silver iodide in Neo Silvol) with suitable diluents. They are not astringent nor irritant, and are used as mild local antiseptics. They have the advantage of being colorless.

Actions and Uses.—The colloidal silver compounds are used mainly on mucous membranes, for antiseptics. The strong protein silver group is most effective in this respect, but is slightly irritant and stimulant. The mild protein silver group acts largely as mucilaginous demulcent and protective, and as detergent, by dislodging pus. Collargol acts locally like the protein silver, mild group, but is used mainly to produce systemic reactions.

Eye	Strong Protein Silver Per Cent	Mild Protein Silver Per Cent
Conjunctivitis simple purulent or gonorrheal	2 to 10	Solution 25 Ointment 10
Prophylaxis against ophthalmia neonatorum	2 to 10	25
Prophylaxis before ophthalmic operations (several days)		25
Corneal ulcers		50
Nose and throat	0.5 to 10	Spray 10 to 20 Swab 25 to 50
Wounds and ulcers		1 to 10 solution 10 dusting powder
Gonorrhea		
Injections—prophylactic	2	10
Gynecologic practice		
Solutions	2 to 10	25 (tampons of solution in glycerin)
Tampons	2	
Ointments	5	
Suppositories	5	Suppositories 20 (0.3 Gm.)
Rectal administration		
Injection	2	10
Suppositories	5 to 10	20 (0.13 Gm.)
Pyelography		2 (solkargol) 50 (cargentos)

The antiseptic efficiency of the silver compounds and their content of silver ions may be conveniently compared by their restraining effect on gas formation by yeast according to the method of Dreser, as modified by Pilcher and Sollmann (*J. Lab. & Clin. Med.* 8:301, 1923). According to this the following solutions approximately equal the efficiency of a 1 in 1000 solution of silver nitrate in the same media (*J. Lab. & Clin. Med.* 9:260, 1924): protargol in water 1 per cent, in physiological solution of sodium chloride 0.125 per cent, in blood 0.9 per cent, and silvol in water 36 per cent in physio-

logical solution of sodium chloride 1 per cent in blood 3 per cent

Dosage—The concentrations for mucous membranes range from 0.1 to 10 per cent for strong protein silver, from 5 to 50 per cent for mild protein silver and from 0.02 to 1 per cent for collargol. These are applied every two to four hours if possible. Solutions should be recently prepared, and should be protected against light. Ointments and suppositories are used with the same concentrations as the aqueous solutions. Stains on linen are removed by 1 in 1000 solution of mercuric chloride. The usual concentration for special purposes are shown in the adjoined table.

Since the advent of the sulfonamide compounds and of penicillin the use of silver salts for the treatment of gonorrhea, cystitis, sinusitis and in gynecologic practice has decreased enormously. Moreover the physician using silver salts must constantly keep in mind the possibilities of later argyria. *Because of the danger of absorption and possible production of argyria solutions of silver salts should not be used for irrigation of the bladder of the vaginal tract or of the intestinal tract.*

(Early Preventive) Treatment of Venereal Diseases—The ordinary routine consists in washing the parts thoroughly with soap and water after which a 2 per cent strong protein silver solution is injected into the urethra and held there for five minutes. The glans is then injected with 30 per cent mild mercurous chloride ointment for five minutes.

The efficacy has been marked if the treatment is applied thoroughly within an hour after exposure and is fair up to three hours. In the A. E. F. of World War I the ratio of diseases to exposure was about 1 in 30 without prophylactic treatment and 1 in 90 with treatment. Prophylaxis therefore reduced the incidence to about one third (Ashburn 1919). It is practically useless after five hours.

LUNOSOL	of colloidal silver
10 Gm.	about 10 Gm.
1 Gm.	and water

and 1 to 10 Gm.

Actions and Uses—Lunosol liquid has antiseptic and germicidal properties. Even undiluted it causes neither irritation of the mucous membranes nor coagulation of albumin. It does not stain the skin on topical application. Possibilities of argyria from its continued use must constantly be kept in mind.

Lunosol liquid is intended for prophylaxis against and treatment of infections of the accessible mucous membranes such as the genito-urinary tract and the eye, ear, nose and throat.

Dosage—Lunosol liquid is generally used in solutions (colloidal suspensions). In the male urethra from 3 to 25 per cent, in the genito-urinary tract of the female 5 to 25 per cent in

inflammatory infections of the eye, ear, nose and throat, 10 to 100 per cent, in otitis media neonatorum, 25 to 100 per cent solutions are applied

Tests and Standards—

Lunosol (liquid) is a milkwhite syrup colorless having a sweet metallic taste

If a solution of 0.5 cc of lunosol in 25 cc of water is treated with 0.6 gm of potassium iodide dissolved in a few cc. of water, a yellow liquid is formed. If 0.5 cc of lunosol is dissolved in 25 cc of water and 8 cc of strong ammonia water is added a clear colorless solution results. If a solution of 0.5 cc of lunosol in 10 cc of water is treated with 15 cc of tenth normal sodium thiosulfate a clear colorless solution results. Place a few drops of lunosol solution (1 in 10) in the nostril; no sensation of irritation is produced. To about 2 cc of fresh undiluted egg white add 1 cc of lunosol solution (1 in 10); shake the mixture, then allow to stand for fifteen minutes and finally dilute with 15 cc of water, no precipitate forms.

Dissolve approximately 0.5 cc of lunosol, accurately measured in 25 cc of water, add 8 cc of stronger ammonia water followed by an excess of nitric acid. Collect, wash, dry and weigh the precipitate. The weight of silver chloride found corresponds to a content of not less than 9.5 nor more than 10 per cent of silver chloride in the specimen taken.

UNIT LABORATORIES

Liquid Lunosol. An aqueous solution containing 100 Gm of lunosol in each 100 cc (1 cc of liquid lunosol is equivalent in silver chloride content to 1 Gm of lunosol) marketed in $\frac{1}{2}$ and 2 ounce dropper bottles accompanied by an empty dilution bottle thus affording a convenient means of preparing the various dilutions which may be indicated, also in 1 ounce and 4 ounce bottles for dispensing.

Lunosol Ointment, 10 per Cent. Lunosol liquid, 10 cc., incorporated in 90 Gm of an unguent base composed of about 17 Gm of water, 55.5 Gm of anhydrous lanolin and 27 Gm of liquid petrolatum in each hundred grams.

U. S. trademark 189347

MILD PROTEIN SILVER—Mild Silver Protein—Mild Protargin— Silver rendered colloidal by the presence of, or combination with, protein. It contains not less than 19 per cent and not more than 23 per cent of silver (Ag). U. S. P.

"Caution—Solutions of Mild Protein Silver should be freshly prepared and should be dispensed in amber colored bottles." U. S. P.

For description and standards see the U. S. Pharmacopeia under Mild Protein Silver.

Actions, Uses and Dosage—See preceding article, Colloidal Silver Preparations. Possibilities of argyria from its continued use must constantly be kept in mind.

ABBOTT LABORATORIES

Argyn (Powder) 30 Gm 120 Gm and 453 Gm bottles
A colloidal compound of silver oxide and serum albumin

U S trademark 117 522

Argyn Tablets 0.39 Gm

PARKE DAVIS & COMPANY

Silvol (Powder) bulk A colloidal compound of silver with an alkaline protein

Capsules Silvol 0.39 Gm

Vaginal Suppositories Silvol 5 per Cent Suppositories weighing 845 Gm and containing silvol 5 per cent in a base composed of gelatin and glycerin

F R SQUIBB & SONS

Solargentum Powder 120 Gm and 453 Gm bottles

Tablets Solargentum 0.3 Gm A colloidal compound of silver and gelatin

U S trademark 318 686

NEO SILVOL — Colloidal silver iodide compound — A compound of silver iodide with a soluble gelatin base containing 18 to 22 per cent of silver iodide in colloidal form

Actions and Uses—Neo silvol even in concentrated solutions causes neither irritation of mucous membranes nor coagulation of albumin. It does not stain the skin on topical application. Possibilities of argyria from its continued use must constantly be kept in mind.

Neo silvol is intended for prophylaxis against and treatment of infections of accessible mucous membranes especially of the genito urinary tract and of the eye ear nose and throat.

Dosage—In the treatment of acute inflammations of the mucous membranes solutions of neo silvol as strong as 50 per cent may be used. In inflammatory infections of the ear, nose and throat 5 to 40 per cent solutions are used for irrigating sinuses 2 to 5 per cent for inflammatory conditions of the eye and conjunctival infections a strength of 10 to 40 per cent as urographic medium 20 per cent.

Solutions of neo silvol are prepared by adding the substance to the required amount of water (not for concentrations of 25 per cent or over) and agitating the mixture until solution occurs.

Solutions tend to precipitate gradually after standing longer than a week. Local anesthetics should not be added to solutions of neo silvol.

Tests and Standards.—

Neo-silvol is prepared by heating freshly precipitated silver oxide with gelatin (which has been previously dissolved in a dilute alkaline solution) until the silver oxide has been reduced to a metallic silver in a colloidal state of subdivision. The solution is treated with iodine, which combines with the silver. The liquid is then evaporated to dryness *in vacuo*. The finished product contains from 1 to 3 per cent of combined iodine in excess of that required for combination with the silver.

Neo silvol occurs as pale yellow granules. In concentration up to 50 per cent neo silvol forms with water almost colorless, milky or opalescent solutions (*colloidal suspensions*). Neo-silvol is insoluble in fixed oils, but slowly soluble in glycerin. Solutions of neo-silvol are not precipitated in the cold by strong acids or sodium chloride.

If a solution of neo-silvol is treated with a solution of potassium hydroxide no precipitate of silver iodide is formed; if this solution is boiled for a few minutes, it darkens gradually, but no precipitate is formed unless it is allowed to stand for some time. If a solution of neo-silvol is treated with dilute hydrochloric acid silver iodide is not precipitated; if this mixture is now boiled, the silver iodide is gradually precipitated. Dilute solutions of neo silvol do not discolor in sun light (*absence of silver chloride and silver bromide*).

Transfer about 1 Gm. of neo silvol granules weighed to an 8 ounce bottle, add 100 cc. of 10 per cent hydrochloric acid (U. S. Pharmacopoeia). Boil for 10 minutes, and weigh as silver iodide. The weight found is equivalent to 18 to 22 per cent of silver iodide.

PARKE, DAVIS & COMPANY

Neo-Silvol (*Granules*): bulk.

U. S. patent 1,610,391 (Dec. 14, 1926; expired). U. S. trademark 157,369.

Capsules Neo-Silvol: 0.39 Gm.

Neo-Silvol Ointment, 5 per Cent: Neo-silvol, 5 per cent, in a base composed of glycerin, benzoinated lard, hydrous wool fat and petrolatum.

Neo-Silvol Vaginal Suppositories: Neo-silvol, 0.454 Gm in a base composed of gelatin, glycerin and water.

STRONG PROTEIN SILVER.—Strong Silver Protein—Strong Protargin—Contains not less than 75 per cent and not more than 85 per cent of silver (Ag). U. S. P.

"Caution—Solutions of Strong Protein Silver should be freshly prepared and should be dispensed in amber-colored bottles." U. S. P.

For description and standards see the U. S. Pharmacopoeia under Strong Protein Silver.

Actions, Uses and Dosage—See preceding article, Colloidal Silver Preparations. Solutions are best prepared by dusting the powder on the surface of cold water, and allowing it to dissolve.

without stirring or shaking. This requires about ten minutes. Solutions should be freshly prepared. Possibilities of argyria from its continued use must constantly be kept in mind.

MERCK & CO., INC.

Silver Protein Strong (*Powder*) bulk

WINTHROP CHEMICAL COMPANY, INC.

Protargol (*Powder*) 30 Gm bottle. A colloidal compound of silver albumose.

U. S. trademark 30 882

Granules Protargol Compound 30 Gm bottle. Protargol 33½ per cent and urea 66½ per cent added to increase the solubility.

Silver Salts

SILVER LACTATE — *Argentis Lactas* — $\text{Ag C}_6\text{H}_5\text{O}_2 + \text{H}_2\text{O}$ — The silver salt of lactic acid.

Actions and Uses — Silver lactate is used as an active antiseptic. It is irritating if applied in substance to wounds. Possibilities of argyria from its continued use must constantly be kept in mind.

Dosage — From 1 in 100 to 1 in 2 000 solutions.

Tests and Standards —

Silver lactate is prepared by dissolving freshly precipitated silver carbonate in solution of lactic acid by the aid of heat and concentrating the solution until crystallization begins. The operation must be conducted in a darkened room.

Silver lactate occurs in the form of crystalline needles, granular masses or crystalline powder. It dissolves in about 15 parts of water. Silver lactate when heated leaves a residue of metallic silver weighing 50.0 to 51.5 per cent. It is usually colored somewhat brown and gives with water a brownish or reddish solution. The salt must be protected from the light.

MERCK & CO., INC.

Silver Lactate (*Crystals*) bulk

SILVER NITRATE — When powdered and dried to constant weight in the dark over sulfuric acid contains not less than 99.8 per cent of AgNO_3 . U. S. P.

For description and standards see the U. S. Pharmacopeia under Silver Nitrate.

ABBOTT LABORATORIES

Silver Nitrate Solution, 1 per Cent. 0.5 cc. wax ampul

ARZOI CHEMICAL COMPANY

Silver Nitrate Applicators Silver nitrate 75 per cent and potassium nitrate 25 per cent fused to one end of 3 inch and 6 inch wooden sticks. Each applicator is to be used but once.

PARK, DAVIS & COMPANY

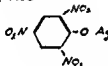
Capsules Solution Silver Nitrate, 1 per Cent 0.4 cc paraffin lined beeswax capsules

U. S. patent 1,527,659 (Feb. 24, 1925, expired)

SHARP & DOHMEYER INC.

Solution Silver Nitrate, 1 per Cent 0.2 cc beeswax ampul

SILVER PICRATE—Picragol—Silver trimethylphenolate
 $-\text{C}_6\text{H}_3(\text{OAg})(\text{NO}_2)_3 + \text{H}_2\text{O}$



Actions and Uses—Silver picrate has actions and uses similar to those of the other simple silver salts. Its crystals are available for treatment of glands by the aqueous solution.

The aqueous solution of silver picrate may be used in the treatment of gonorrheal vaginitis in children. It is also used in the form of a compound powder in the treatment of vaginitis due to *Trichomonas vaginalis* and *Monilia albicans*. This compound powder contains 1 per cent silver picrate in purified kaolin. It is administered by means of an insufflator or other surgical powder blower. Another dosage form is intended primarily to be used as an adjunct in the treatment of this condition—vaginal suppositories containing 0.13 Gm. in a boroglyceride gelatin base. Prolonged use of this compound over a long period may possibly give rise to argyria because of its silver content and nephritis because of its picric acid content. It is therefore necessary to watch the skin for signs of argyria and the urine for albumin and casts. Possibilities of argyria from its continued use must constantly be kept in mind. In all vaginal insufflation in the pregnant female the physician should exercise every precaution to prevent positive pressure in the vagina because of danger of breaking the enlarged veins and introducing air into the venous circulation.

Dosage—Dilutions of from 1 to 2 per cent are used in the form of solution, compound powder and vaginal suppositories.

Tests and Standards—

Silver picrate occurs as yellow crystals, slowly discoloring in sun light. It is sparingly soluble in water and alcohol, slightly soluble in

Dissolve an accurately weighed quantity of the material in water,

at 120 C. the amount of silver calculated from the silver chloroform found corresponds to not less than 30 per cent, nor more than 32 per cent

WYETH, INCORPORATED

Picragol Crystals: 2 Gm. bottle

Compound Picragol Powder, 1 per Cent. Silver picrate, 1 per cent, in purified kaolin

Picragol Vaginal Suppositories: 65 mg. (infant size) and 0.13 Gm. Silver picrate in a boroglyceride gelatin base

Peroxides

Hydrogen peroxide is a combination of two atoms of hydrogen with two atoms of oxygen, one of the latter being given off to oxidizable substances, leaving a residue of water. In the presence of catalase, a ferment found in all cells, it is readily decomposed. The liberated oxygen sometimes causes considerable effervescence. For this reason it is dangerous to inject it into closed body cavities or into abscesses from which the gas has not a free exit. Hydrogen peroxide solution (liquor

readily decomposed with liberation of hydrogen peroxide, or of oxygen.

*Actions and Uses—*Like hydrogen peroxide, the metallic peroxides depend for their value on the readiness with which a part of their oxygen becomes active. They are claimed to possess advantages over solution of hydrogen peroxide, because the oxygen is set free more gradually. Among themselves the metallic peroxides differ in their action in accordance with their solubility and the alkalinity produced by interaction of

the peroxide with water. The action of peroxides is also affected by the nature of the metal which goes into solution when the peroxide is decomposed. Thus the use of sodium peroxide is limited by the strong base formed when it dissolves in water.

Aqueous suspensions of zinc peroxide have been found useful in the local treatment of certain wound infections such as those caused by microaerophilic or anaerobic organisms. Infections caused by some aerobes including hemolytic streptococci have also responded to such treatment.

Because of the strong oxidizing effects on the lower organisms the peroxides have been recommended as a convenient means of sterilizing water.

SODIUM PEROXIDE—*Sodii Peroxidum* — Na_2O_2 —The sodium compound analogous to hydrogen peroxide containing at least 90 per cent of sodium peroxide.

Actions and Uses—Sodium peroxide is not used internally but has been used in acne applied in the form of a paste prepared with liquid paraffin or as a soap to remove comedones.

Tests and Standards—

Sodium peroxide occurs in the form of a white or yellowish amorphous powder. It is soluble in water with decomposition and evolution of heat forming an alkaline solution and liberating oxygen. It dissolves in cold dilute acids forming a solution of hydrogen peroxide.

It resumes its ether on pressure on

chlorides of sodium made up to the normal less than

90 per cent sodium peroxide

MERCK & CO. INC.

Sodium Peroxide (Powder) bulk. Contains not less than 96 per cent of sodium peroxide.

ZINC PEROXIDE MEDICINAL—Consists of a mixture of zinc peroxides, zinc oxide and zinc hydroxide. It contains not less than 45 per cent of ZnO_2 . —U. S. P.

For description and standards see First Bound Supplement U. S. Pharmacopeia VII under Medicinal Zinc Peroxide.

Actions and Uses—See general article Peroxides.

Dosage—Zinc peroxide medicinal (powder) sterilized in small quantities (10 to 50 Gm.) by heating in a dry oven for four hours at exactly 140°C is made up with sterile distilled water to a smooth creamy suspension of about the consistency of heavy (40 per cent) cream. The dose depends entirely on the size of the wound to be treated. Enough of the creamy

suspension should be used to provide the surface of the wound with a layer approximately $\frac{1}{8}$ inch thick. If the suspension is too thin it runs off. If it is too thick it may not come in contact with all surfaces in the crevices of the wound. The suspension should be a cream and not a paste. The first layer, applied readily with a syringe is then covered over with a thin layer of cotton soaked in the suspension and this in turn covered with a thick layer of cotton wet with water and then sealed with an impermeable covering or coating of some kind. Dressings are usually changed in twenty four hours but may be left for several days.

WALLINGKRODT CHEMICAL WORKS

Zinc Peroxide 45%, ZnO_2 Medicinal (Powder) 30 Gm
113 Gm and 453 Gm bottles

MERCK & Co, INC

Zinc Peroxide Special Medicinal (Powder) 15 Gm
30 Gm 113 Gm and 453 Gm bottles

Pyrethrum Preparations

PYRETHRUM OINTMENT—An ointment containing an extract from powdered pyrethrum flowers (*Chrysanthemum cinerariaefolium*). The extract is obtained by treating powdered pyrethrum flowers with a hydrocarbon oil of the kerosene type. This extract is then incorporated into an ointment base composed of hydrous wool fat, petrolatum and paraffin. The finished ointment contains 27 per cent of the active extract (representing 0.75 per cent of pyrethrins I and II) and 73 per cent of ointment base.

Actions and Uses—Pyrethrum ointment. Upsher Smith has

ment of scabies
dder (Minnesota
Lancet 56 467,
etrates the bur
and that except

in rare instances it does not produce dermatitis with resultant exfoliation. Sweitzer and Tedder reported four cases of allergic sensitivity to the active substance in a series of 618 patients treated.

Dosage—The ointment is applied to the entire body following a thorough cleansing with soap and water. Further applications are made on at least three or four successive days. In most cases it is necessary to continue the treatment for a period of from five to seven days and in obstinate cases the use of the ointment may be required for a longer time. The ointment should not be used on patients who are sensitive to pyrethrum flowers.

Tests and Standards—

Pyrethrum ointment is an unctuous yellowish green mass

Place 5 Gm of pyrethrum ointment in a suitable flask, add 25 cc of half normal potassium hydroxide alcoholic solution and an equal volume of water and heat the mixture under a reflux condenser for five minutes. The alcohol is removed by evaporation, the mixture

liquid by decantation, add mix and allow to separate, to remove the excess of add an equal volume of mercuric sulfate solution, an immediate pink color develops which deepens on standing finally changing to a green coloration with the development of a turbidity or a precipitate (*monocarboric acid*)

Determine the pyrethrin content by the procedure (with slight modification) described by Seil in 'Soap' in May 1934, the combined pyrethrin content (pyrethrins I and II) is not less than 0.75 per cent nor more than 1 per cent

UPSHER SMITH COMPANY

Pyrethrum Ointment: 100 Gm and 27 Kg containers

Resorcin Compounds

RESORCINOL MONOACETATE—Euresol—Resorcin Acetate, *m*-Hydroxyphenyl Acetate—*m*-Acetyloxyphenol $C_6H_4(OH)(OOCCH_3)$ The monoacetic ester of resorcinol

*Actions and Uses—*The action of resorcinol monoacetate is similar to that of resorcinol, but milder and more lasting because of the gradual liberation of resorcinol. Moreover, resorcinol monoacetate in contrast to resorcin does not give a greenish tint to light or gray hair

Resorcinol monoacetate is used as an adjuvant in the treatment of acne, of sycosis vulgaris, of alopecia and of seborrhea

*Dosage—*Resorcinol monoacetate is applied in ointments of from 5 to 20 per cent and in acetone solution. For scalp lotions alcohol solutions of from 3 to 5 per cent of resorcinol monoacetate are used

Tests and Standards—

Resorcinol monoacetate is a viscous lemon yellow liquid boiling under ordinary pressure at 283 C with decomposition. It is soluble in alcohol, acetone and most organic solvents, sparingly soluble in water. It has a faint characteristic odor and burning taste. Resorcinol monoacetate at a pressure of 10 mm, distills completely between 150 and 153 C

Dissolve 10 cc resorcinol monoacetate in 20 cc benzene and shake with 100 cc of distilled water containing methyl orange solution not more than 0.5 cc tenth normal alkali is required to neutralize the free acidity

BILHUBER KNOIL CORP

Euresol pro Capillis Resorcinol monoacetate with isopropyl alcohol 6 per cent, perfumed to render it suitable for scalp lotions

U S trademark 88 894

HOFFMANN LAROCHE, INC

Thigenol (*Liquid*) bulk.

U S trademark 80 424

Ethylhydrocupreine

Ethylhydrocupreine is a synthetic derivative of cupreine $C_{11}H_{21}O_2N_2$. Cupreine is an alkaloid occurring together with quinine in the bark of *Remijia pedunculata*. Ethylhydrocupreine may also be synthetically made from quinine. It is closely related to quinine differing from the latter in containing two more hydrogen atoms and an ethoxy group in place of a methoxy group. Ethylhydrocupreine has the antimalarial and anesthetic action of quinine. Toxic symptoms however, such as tinnitus deafness amblyopia or amaurosis (retinitis) are more liable to occur than with quinine. While these are generally transient retinitis may result in permanent impairment of vision. This demands caution in the administration of the drug. Ethylhydrocupreine has a specific bactericidal effect on the pneumococcus in vitro and it exerts a protective and curative action in animals experimentally infected with virulent strains of pneumococci. The value of the drug in the internal treatment of lobar pneumonia in man has not been established. Ethylhydrocupreine hydrochloride has a definite value in the treatment of pneumococcic infections of the eye (ulcus corneae serpens).

ETHYLHYDROCUPREINE HYDROCHLORIDE—

Optochin Hydrochloride—Contains when dried for 24 hours over sulfuric acid not less than 90 per cent of ethylhydrocupreine base ($C_{11}H_{21}O_2N_2$) —A 1

For description and standards see the National Formulary under Ethylhydrocupreine Hydrochloride

Actions and Uses—See preceding article Ethylhydrocupreine

Dosage—For application to the eye and instillation into the conjunctival sac a freshly prepared 1 or 2 per cent solution is used. It is not recommended for oral administration

RARE CHEMICALS, INC

Optochin Hydrochloride (*Powder*) bulk

U S patent 1 060 203 (May 20 1913 exp red) U S trademark 343 326

Tablets Optochin Hydrochloride 0.1 Gm

CHAPTER V

SYSTEMIC ANTI-INFECTIVES

Antibacterial Agents

Chaulmoogra Derivatives

In the U. S. Pharmacopœia are described chaulmoogra oil and ethyl chaulmoograte. Chaulmoogra oil has been used in the treatment of leprosy for many years. The evidence behind this use indicated that it might be of possible value, though not having specific curative properties. However, experienced observers consider the oil and its derivatives valueless in the treatment of leprosy. Further cases for treatment with this drug and its derivatives must be selected with great care or much harm may be done. The Council on Pharmacy and Chemistry has given consideration to the status of these agents and is of the opinion that the evidence now available does not support claims for the use of chaulmoogra oil and its derivatives for the treatment of leprosy. However, ethyl chaulmoograte has been found to be of definite value in sarcoidosis (Schammann's Disease) formerly spoken of as Boeck's Sarcoid.

Gold Compounds

GOLD SODIUM THIOSULFATE—*Sodii et Auri Thio-sulfas*—Sodium Gold Thiosulfate—Sodium Aurothiosulfate, $\text{Na}_2\text{Au}(\text{S}_2\text{O}_3)_2 \cdot 2\text{H}_2\text{O}$. The complex salt formed from 1 molecule of gold thiosulfate and 3 molecules of sodium thiosulfate. It contains approximately 37.4 per cent of gold.

Actions and Uses—A review of the literature in regard to

in cases originally thought cured nevertheless the beneficial and often curative action of the drug in a fair percentage of the cases seems to warrant giving it a definite place in the treatment of a disease for which at present there is no specific remedy.

Gold salts have also been recommended for use in the treatment of rheumatoid arthritis. The Council takes the viewpoint that until more convincing reports of their value have been presented this therapy must be considered to be still in the

extreme caution
culosis and in
first advocated
have been found to be too great, resulting frequently in severe

reactions, sometimes resulting fatally. Even with much smaller doses, accidents of this kind have occurred. The reactions most commonly encountered are varying degrees of fever, diarrhea, vomiting, albuminuria, enteritis, stomatitis, prostration and shock. Skin reactions consist of varying degrees of erythema, urticaria, severe papular and vesicular dermatitis, and scarlatiniform and exfoliative dermatitis. Cases of aplastic anemia of hemorrhagic diathesis, and of agranulocytosis have also been noted following its use. Published necropsy reports reveal conditions usually found in heavy metal poisoning. A certain number of cases of toxic hepatitis and of acute yellow atrophy have been noted after the use of this drug, likewise isolated cases of generalized pigmentations. Patients to whom gold salts are being administered should be warned of possible deleterious effects from strong sunlight. Moreover, they should not be given actinotherapy.

Dosage—At present the initial dose preferred is 5 mg intravenously or intramuscularly given in from 2 to 5 cc of sterile distilled water. Subsequent doses given at weekly intervals are increased 5 mg per dose not exceeding a maximum of 50 mg for women and 75 mg for men, provided no reactions have occurred. The drug may be continued cautiously in smaller dosage followi but should be discontinued if severe reactions have occurred. A careful patient should be given the liver and kidneys, be made before using. The acute disseminated type are most likely to show an extreme idiosyncrasy for the drug, and use of the drug is unwise in these cases.

Sodium gold thiosulfate occurs in white, glistening needle-like or prismatic crystals. The aqueous solution is colorless. It is freely soluble in water, very slightly soluble in alcohol, ether and chloroform. An aqueous solution (1:200) is neutral or faintly alkaline to litmus.

Sodium gold thiosulfate decomposes without melting when heated gently leaving a brown residue on ignition. An aqueous solution (1:200) assumes a yellow color.

Dissolve 0.1 Gm. of sodium gold thiosulfate in separate portions of 2 cc. of silver nitrate solution, precipitate on addition of 0.2 cc. of ammonia water and 0.5 cc. of solution of hydrogen peroxide followed by heating to boiling point (distinction from arsenic antimony and tin) no precipitate with

after heating with 0.4 cc. of sodium bisulfite solution (no auric compounds).

Dissolve about 0.5 Gm. of sodium gold thiosulfate accurately weighed in 5 cc. of water carefully add 4.5 cc. nitric acid and 25 cc. water, agitate, when the reaction has subsided filter the residue onto a tared Gooch crucible. Wash the residue with six 25 cc. portions of water and save the filtrate for determination of sulfur constituent.

Wash the residue in the crucible with alcohol and ether after removal of the filtrate, dry the contents at 100 C and ignite to constant weight. The weight of gold should not be less than 37 per cent nor more than 37.5 per cent.

Transfer the filtrate from the gold precipitation to a 250 cc volumetric flask and make up to volume by addition of water. Pipet 50 cc of the solution to a 500 cc beaker, add 5 cc hydrochloric acid

ABBOTT LABORATORIES

Gold Sodium Thiosulfate 10 mg, 25 mg, 50 mg, 75 mg, 0.1 Gm, 0.25 Gm ampuls

MERCK & Co, Inc

Gold Sodium Thiosulfate 10 mg, 25 mg, 50 mg ampuls and 100 mg bottles

G. D. SEARLE & Co.

Solution Gold Sodium Thiosulfate with Sodium Thiosulfate and Benzyl Alcohol 2% V/V. 5 cc ampuls containing gold sodium thiosulfate 50 mg, sodium thiosulfate U. S. P. 278 mg, sodium sulfite 83 mg and benzyl alcohol 2 per cent.

TRIPHAL—A product consisting essentially of sodium aurothiobenzimidazole carboxylate, $C_6H_4N-NHCSAuCOONa$ with a small amount of a product of indefinite composition. The sodium salt of a compound formed by the interaction of gold halides with thiobenzimidazole carboxylic acid. Triphal contains from 44 to 47 per cent of gold.

Actions and Uses—Proposed for use as a gold salt in the treatment of lupus erythematosus. Foci of infection, if present, should be removed before beginning treatment with triphal. It is contraindicated in pregnancy, kidney disease, acute progres-

erythema or albuminuria indicates intolerance to the drug, on its appearance triphal should be discontinued.

Dosage—For adults, initial dose, intravenously, 5 mg, the dose being gradually increased to 75 mg, for children average initial dose, 0.5 mg, gradually increased, if possible, to 25 mg once a week.

Tests and Standards—

Triphal occurs as a light yellow, odorless powder, readily soluble in cold water, insoluble in alcohol and ether. An aqueous solution of triphal is slightly alkaline in reaction, is stable for only a short time.

and is readily decomposed by heat. On addition of mineral acids to solution, a precipitate is produced, soluble on addition of excess alkali solution.

Dissolve 0.1 Gm triphal in 1 cc water, a clear solution results. Transfer 1 cc of triphal solution (1:200) to a clean test tube containing a freshly prepared solution of sodium stannite (prepared by

to 2 cc of dekanormal sodium
barely dissolves) Gently heat
the mirror is formed. To 3 cc
mal sodium hydroxide solution
ydrazine hydrochloride solution

(1:10), a blue color is produced which appears reddish in reflected light. To 4 cc of the solution (1:200) add 0.15 cc alkaline mercuric

potassium iodide solution a pronounced yellowish color is produced.

Dissolve 0.1 Gm of triphal in 3 cc water, add 0.2 cc of diluted acetic acid, and filter. The filtrate shows no brown coloration after adding

0.1 cc of sodium sulfide solution. To 2 cc of solution (1:50) add

0.2 cc diluted nitric acid and filter, to one half of the filtrate add 0.2

cc barium nitrate solution; no precipitate occurs (sulfate), to the

other portion of acidified solution add silver nitrate solution not more

than a faint turbidity appears (halides). To 4 cc of triphal solution

(1:100) add 0.2 cc sodium nitrite solution and 0.2 cc diluted hydro-

chloric acid followed by the addition of sufficient betanaphthol solution

(0.01 Gm in 5 cc of sodium hydroxide solution) that the precipitate

formed redissolves, no red color appears. Ignite 0.1 Gm of triphal

in a porcelain crucible, extract the residue with normal hydrochloric

acid and filter, the filtrate gives a characteristic sodium flame test

and yields a white precipitate with a solution of barium chloride.

Dry about 0.1 Gm of triphal accurately weighed for eight hours

at 100°C. The loss in weight should not be more than 8.0 per cent

nor less than 6.0 per cent of sample weight.

Transfer approximately 0.2 Gm triphal accurately weighed into a

dried porcelain crucible, and ignite well at red heat. Extract the

residue with six 5 cc portions of normal hydrochloric acid solution.

Filter each portion through an ashless filter paper. Transfer the

remaining residue to the filter and wash with five 3 cc portions of

water. Transfer filter and residue to crucible, dry, and ignite to

constant weight. The weight of the residue corresponds to not more

than 50.0 per cent and not less than 47.8 per cent of gold, calculated

to the dried basis.

WINTHROP CHEMICAL COMPANY, INC.

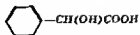
Triphal 25 mg and 0.1 Gm ampuls

U S patent 1,558,584 (Oct 27, 1925, expired)

U S trademark 188,475

Mandelic Acid Preparations

MANDELIC ACID—Racemic Mandelic Acid—'When dried over sulfuric acid for 18 hours, contains not less than 99 per cent of $\text{HC}_6\text{H}_5\text{O}_2$.' U S P Mandelic acid has the following structural formula



For description and standards see the U S Pharmacopeia under Mandelic Acid.

Actions and Uses—Mandelic acid is a nonmetabolizable substance which when administered by mouth is excreted unchanged in the urine and if the pH of the urine is kept at 5.5 or less it is rendered bactericidal or bacteriostatic against *Escherichia*

coli Aerobacter
of the Proteus
Shigella groups
determinations o
reduced to pH

ammonium chloride ammonium nitrate or nitrohydrochloric acid may be administered concurrently providing there are no contra indications For the same purpose the ketogenic diet has also been employed Fluid intake should be restricted to an amount not exceeding 1200 cc daily It is usually neither necessary nor advisable to continue mandelic acid therapy longer than from twelve to fourteen days as renal irritation may ensue Nausea diarrhea dysuria and hematuria may also occur occa

may occur from retention of the acid

Dosage—The usual dosage is 3 Gm four times a day either as the free acid or in the form of the sodium or ammonium salt An additional acidifying agent is usually required when the sodium salt is employed

GANE AND INGRAM, INC

Mandelic Acid (Powder) bulk

MALLINCKRODT CHEMICAL WORKS

Mandelic Acid (Powder) bulk

MERCK & Co, INC

Mandelic Acid (Powder) bulk

SYRUP OF AMMONIUM MANDELATE—A syrup containing approximately 40 Gm of mandelic acid and approximately 45 Gm of ammonia per hundred cubic centimeters It contains ammoniated glycyrrhizin anethol or menthol and other flavoring agents and is sweetened with sugar and saccharin

Actions and Uses—Ammonium mandelate is used to provide mandelic acid therapy without concurrent use of ammonium chloride as a urine acidifier In some cases supplementary therapy with ammonium chloride is necessary

Dosage—The daily dose for adults should provide 12 Gm of mandelic acid administered in divided doses

Tests and Standards—

Syrup of ammonium mandelate occurs as a dark brown viscous liquid possessing a characteristic odor and a bitter taste with a sweet lcor ce lke after taste The pH of syrup of ammonium mandelate is not below 5.0 nor above 7.0 the specific gravity is between 1.2 and 1.4

Transfer 2 cc of syrup of ammonium mandelate to a separator add 5 cc of water 5 cc of diluted sulfuric acid and extract the mixture with 25 cc of ether filter the ether solution through a cotton

plug and evaporate the ether in a stream of warm air the melting point of the residue is from 118 to 120 C and it responds to the tests of identity for mandelic acid U S P Warm 2 cc of syrup of ammonium mandelate with 5 cc of sodium hydroxide solution a strong odor of ammonia is evolved Ash 1 Gm of syrup of ammonium mandelate the residue found is not more than 0.1 per cent

Transfer an accurately weighed portion of syrup of ammonium mandelate equivalent to about 20 cc of the syrup to a 500 cc calibrated flask dilute to the mark with water and mix thoroughly

Transfer 25 cc, accurately measured of the prepared solution to an automatic extractor (liquid liquid), acidify with 5 cc of diluted sulfuric acid and extract with ether for four hours When the extraction is complete evaporate the ether extract to a volume of about 10 cc, and finally complete the removal of ether in a stream of air Add 25 cc of neutral alcohol and titrate with tenth normal sodium hydroxide using phenolphthalein as the indicator The amount of mandelic acid found corresponds to not less than 39 per cent (W/V) nor more than 41 per cent (W/V) of the undiluted syrup

WYLLI INCORPORATED

Syrup Ammonium Mandelate 480 cc bottles, accompanied by a supply of chlorphenol red test papers

Methenamine Compounds

METHENAMINE — Hexamethylenamine — Hexamethylenetetramine — When dried over sulfuric acid for 4 hours contains not less than 99 per cent of $(CH_2)_6N_4$ U S P

For description and standards see the U S Pharmacopeia under Methenamine and Methenamine Tablets

Actions and Uses—Methenamine owes its action entirely to the liberation of formaldehyde which occurs only in acid fluids It is an active urinary antiseptic provided the urine is secreted in an acid state It has been shown that no antiseptic effects can occur in the body tissue and fluids which have a neutral or slightly alkaline reaction Methenamine is not a uric acid solvent and it has not given satisfactory results in gout As a urinary antiseptic it is used less extensively because there are other more effective agents

Methenamine compounds simply possess the actions of methenamine and of the salts of the acid with which it may be combined

Methenamine may produce urticaria on local application and exceptionally after internal administration The liberation of formaldehyde in the bladder may cause vesical irritation

MERCK & Co, INC

Formin (Powder) bulk

U S trademark 152 230

THE WM S MERRELL COMPANY

Tablets Methenamine 0.325 Gm and 0.5 Gm

SCHERING & GLATZ, INC

Urotropin (*Crystals*) 30 Gm and 453 Gm bottles

Tablets Urotropin 0.3 Gm and 0.5 Gm

U. S. trademark 269 754

WILLIAM R. WARNER & CO., INC

Tablets Methenamine 0.32 Gm and 0.5 Gm

Sulfonamide Compounds

The group of compounds referred to as sulfonamides contain in common the chemical group $-\text{SO}_2\text{N}<$. The therapeutically active members of this group which have been accepted by the Council are derivatives of the sulfonamide called sulfanilamide and are characterized by the group $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{SO}_2\text{N}<$

Actions and Uses—The exact mode of action of the sulfonamide compounds on susceptible bacteria is still uncertain. Experimental evidence indicates that these compounds may interfere with the proper functioning of certain enzyme systems

compounds on certain bacteria, a secondary factor namely the host effect may play a part in ridding the infected individual of invading bacteria. This has been especially studied in the instance of hemolytic streptococcus infections in which it has been demonstrated that the phagocytosis of streptococci noted in the course of sulfonamide therapy of streptococcal infections constitutes an important mechanism in bringing about the complete elimination of the infection. To what extent phagocytosis is important in other infections which are known to be susceptible to sulfonamide therapy has not as yet been established.

It has been demonstrated in vitro that the addition of certain substances to culture media results in a decrease in the growth of bacteria.

many local anesthetics (procaine is a good example) are esters

of para aminobenzoic acid and hence break down in part to the parent substance when injected into the tissues. Pus and necrotic tissue have also been demonstrated to possess anti sulfonamide properties. For this reason it is of importance to remove pus and necrotic tissue before sulfonamides are administered locally.

The choice of the sulfonamide compound which is to be used in the control of known infections should not be based on caprice or elance but on bacteriological diagnosis, experience dictated by knowledge of the experimental therapeutic background of these drugs, their pharmacologic properties in man, their clinical efficacy and finally, the variety, frequency and severity of the toxic reactions which may be produced by the drug.

When all these factors are taken into consideration the following recommendations may be made at the present time concerning the selection of the proper drug for treating a given system infection.

Infection due to	Drug of choice
the drug of choice	"
third and second	"
best treated	"
drug of choice	"
the basis of	"
in the treatment	"
second and	"
infections is	"

should never be used in the treatment of gonococcal infections unless the above mentioned sulfonamide drugs are unavailable. Sulfadiazine or sulfathiazole is the drug of choice in the treatment of staphylococcal infections. Meningococcal infections respond well to therapy with sulfadiazine, sulfathiazole, sulfanilamide or sulfapyridine but current evidence indicates that sulfadiazine is the drug of choice. Sulfadiazine is indicated for use in Friedlander's bacillus infections with sulfapyridine second and sulfathiazole third. *Shigella dysenteriae* and *H. influenzae* infections are among those most likely to respond to sulfadiazine therapy. Recently a number of authors have proposed the oral administration of sulfadiazine for the treatment of gonococcal ophthalmia. It is believed that such use of sulfonamides shortens the period of active infection and diminishes the likelihood of ophthalmic complications.

The clinical evidence as to the effectiveness of sulfonamide compounds in the control of alpha hemolytic streptococcus infections is not completely clear. In tissue infections (other than subacute bacterial endocarditis) produced by the so called mouth varieties of the organism sulfanilamide, sulfadiazine, sulfathiazole and sulfapyridine seem to be about equally effective. None of the sulfonamides are active against the enterococcus group of streptococci. Sulfanilamide is the drug of choice in the treatment of chancroid although other sulfon-

per cent), sulfapyrazine and sulfathiazole may show binding as high as 50 and 75 per cent respectively. These studies have raised a question whether such binding makes the sulfonamide ineffective as an anti-infective agent. The available evidence indicates that the protein does not truly inactivate the sulfonamide. While the drug will not diffuse freely into the tissue when bound to protein, there is no interference from a practical standpoint with clinical response. It should be remembered that even when the sulfonamides are bound to proteins in the blood, they are gradually released with the passage of time. Thus even though one of two compared sulfonamide compounds may have a greater tendency to bind with the plasma protein, any differences in therapeutic effects cannot be attributed solely to such protein binding.

A solution of sulfadiazine has been used with some success in the treatment of burns. It is a colorless, non-staining solution capable of producing an eschar. The burned areas are sprayed at regular intervals for three or four days with the solution until a thin eschar is formed. It should be remembered that such spraying will result in considerable absorption of sulfadiazine and a substantial blood level of the drug. Routine recognized treatment for burns should not be neglected because of the use of this preparation.

Crystalline sulfonamides have been used extensively in the local treatment of certain bacterial infections. Present evidence indicates that crystalline sulfanilamide is highly effective as a topical agent in the therapy of superficial open hemolytic streptococcus infections, while crystalline sulfathiazole is the drug of choice for the local therapy of staphylococcal infections. The incorporation of sulfonamides in ointment bases is still in the stage of clinical investigation; in the light of present information they should never be employed for a longer period than five days because of danger of sensitization of the patient. In the prophylaxis of contaminated wounds, crystalline sulfanilamide is the drug of choice. Crystalline sulfathiazole has been used, but in its present form, and owing to its lower solubility, it has a tendency to cake or crust in wounds, and when this occurs it may act as a foreign body. The use of solutions of sulfadiazine in triethanolamine in the prophylaxis of infection and the treatment of burns is still in the stage of clinical

face of the wound approximately 0.1 gram being used per square inch, but not over 10 grams per person for a 24-hour period.

*Determination of the Sulfonamides in Body Fluids—*It is always desirable to determine the values for the sulfonamides in the blood and body fluids at frequent intervals by the

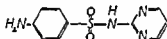
method described by Bratton and Marshall (*J Biol Chem* 128 537 [May] 1939)

Since the dosages suggested below are based on body weight in the metric system the following table of approximations may be convenient for translating pounds into kilograms

11 pounds = 5 kilograms	110 pounds = 50 kilograms
22 pounds = 10 kilograms	132 pounds = 60 kilograms
* 33 pounds = 15 kilograms	154 pounds = 70 kilograms
44 pounds = 20 kilograms	176 pounds = 80 kilograms
55 pounds = 25 kilograms	198 pounds = 90 kilograms
66 pounds = 30 kilograms	220 pounds = 100 kilograms
88 pounds = 40 kilograms	242 pounds = 110 kilograms

O₁S —U S P

Sulfadiazine has the following structural formula



For description and standards see First Bound Supplement U S Pharmacopeia XII under Sulfadiazine and Sulfadiazine Tablets

Clinical Pharmacology—Sulfadiazine resembles sulfapyridine in certain of its pharmacologic effects. When the drug is administered by the oral route its rate of absorption from the gastrointestinal tract is slower and in general less complete than that of sulfathiazole or sulfanilamide. Sulfadiazine is as a rule conjugated to the acetylated form in a lesser degree in the blood and tissues than is sulfanilamide, sulfathiazole or sulfapyridine. It does not pass into the body water as readily as does sulfathiazole or sulfanilamide but it does pass into the cerebrospinal fluid in about the same manner as does sulfanilamide. The drug passes into pleural and abdominal fluids in concentrations of one half to four fifths of those noted in the blood and penetrates the red cells with ease.

It is excreted quite readily by the kidneys in respect both to the drug itself and to its acetylated fraction. Relatively high concentrations of sulfadiazine are easily obtained in the blood of patients to whom the drug is administered because it is not evenly distributed in the tissues of the body. If kidney function is impaired the excretion of sulfadiazine will be reduced and the drug will accumulate in the blood and tissues. The excretion of the drug is generally complete within forty

eight hours after the administration of a single dose of the compound, and in the urine less sulfadiazine is found in the conjugated form than has been noted with sulfanilamide, sulfathiazole or sulfapyridine

Toxicity—The toxic manifestations noted in the course of sulfadiazine therapy are similar to those noted previously in the course of therapy with the other sulfonamide drugs. They are generally unpredictable in their occurrence and are generally the result of an idiosyncrasy to the drug. Patients who are receiving sulfadiazine should be seen daily by their physicians in order that any possible toxic effects arising in the course of its administration may be noted and appropriate steps taken to eliminate the drug.

Sulfadiazine causes fewer toxic reactions than do sulfanilamide, sulfapyridine or sulfathiazole. Nausea, vomiting and dizziness are uncommon. Mental disturbances and psychoses have been described. Peripheral neuritis has not been reported. Cyanosis is rare and acidosis does not occur. Fever and rashes due to the drug are less common than with the other sulfonamide drugs, except sulfaguanidine. Patients receiving sulfadiazine should be kept out of the sun. Injection of the conjunctivas and scleras has been noted. Hepatitis has not been reported but leukopenia with granulocytopenia has been observed early and late in the course of the therapy. Acute agranulocytosis has been noted rarely, occurring during the third week or later of therapy with this drug. Severe hemolytic anemias are rare. Microscopic and gross hematuria have been noted and oliguria and anuria with azotemia have been observed. It is probable that the mechanism responsible for these renal disturbances is the same as that which has been noted previously as producing such complications in the course of sulfapyridine or sulfathiazole therapy. It is important in the course of therapy to keep the urinary output at not less than 1,000 cc daily. When fever, rash, hepatitis, granulocytopenia, acute hemolytic anemia, agranulocytosis, hematuria with oliguria, anuria, injection of the scleras and conjunctivas or other serious toxic manifestations occur, the drug should be stopped and fluids forced in order that sulfadiazine may be eliminated from the body as rapidly as possible.

Dosage—Sulfadiazine is poorly soluble and hence must be administered by the oral route. In adults suffering from pneumococcic pneumonia, severe hemolytic streptococcus infections, severe staphylococcic infections, the initial dose should be of body weight. Then if the pneumococcic pneumonia 10 Gm day and night until the temperature has been normal for seventy two hours. The drug may then be stopped. In severe

streptococcic, staphylococcic and meningococcic infections subsequent doses after the initial doses is 1.0 to 1.5 Gm every four hours day and night until the temperature has been normal for from five to seven days. At this time the drug may be either stopped or continued in smaller doses until the complete recovery of the patient is assured.

In children suffering from pneumonia the initial oral dose should be based on 0.10 to 0.15 Gm per kilogram of body weight and subsequent doses should be one fourth of the initial dose given at intervals of six hours until the temperature has been normal for at least forty eight hours. In severe streptococcic staphylococcic or meningococcic infections in children the drug should be continued until five to seven days of normal temperature have elapsed. Then it may be discontinued or if considered necessary continued in smaller doses until a cure is effected.

In mild or moderately severe hemolytic streptococcus infections an initial oral dose of 0.05 Gm per kilogram of body weight followed by one third of the initial dose given every four hours day and night by mouth until the temperature has been normal for three to five days has been suggested as a satisfactory dosage schedule. All of the above dosages should be controlled if possible by determination of the concentration of the drug in the blood at frequent intervals (see Bratton and Marshall method under Actions and Uses above). In severe streptococcic staphylococcic meningococcic or Friedlander's bacillus infections it is necessary during the febrile period to obtain and maintain concentrations of approximately 15 mg of sulfadiazine per hundred cubic centimeters in the blood of the patients. It is rarely necessary or advisable to attempt knowingly to exceed this concentration of the drug in the blood. In mild or moderately severe streptococcic infections concentrations of the drug in the blood of 5 to 10 mg per hundred cubic centimeters are usually satisfactory.

The incidence of oliguria, hematuria and anuria following sulfadiazine therapy may prove to be great under conditions where the output of urine cannot be maintained above 600 or 800 cc. per day as in tropical climates or where a shortage of water exists. It is recommended that under conditions where such complications are being encountered the medical officers shall administer an initial dose of 4 grams of sodium bicarbonate together with an initial dose of sulfadiazine and shall follow this with 2 grams of sodium bicarbonate every four hours regardless of the dosage of sulfadiazine being employed. In the management of complications resulting from the toxic action of sulfadiazine on the kidneys the administration of even larger doses of alkali such as 3 or 4 grams every four hours, may be helpful.

ABBOTT LABORATORIES

Sulfadiazine (*Powder*) bulk
Tablets Sulfadiazine 0.5 Gm

AMERICAN PHARMACEUTICAL CO. INC.

Tablets Sulfadiazine 0.5 Gm

BUFFINGTON'S, INC.

Tablets Sulfadiazine 0.5 Gm

LEDERLE LABORATORIES, INC.

Sulfadiazine (*Powder*) 120 Gm and 453 Gm packages

Sulfadiazine, 2½% W/V in Ethanolamines Solution (Pickrell) 8 ounce and one pint bottles Sulfadiazine 2.5 per cent in an aqueous medium containing triethanolamine technical 8 per cent w/v with sodium benzoate 0.2 per cent as a preservative

Tablets Sulfadiazine 0.5 Gm

ELI LILLY & CO.

Tablets Sulfadiazine 65 mg and 0.5 Gm

MCNEIL LABORATORIES

Tablets Sulfadiazine 0.5 Gm

THE WM. S. MERRELL COMPANY

Tablets Sulfadiazine 0.5 Gm

PARKE, DAVIS & COMPANY

Tablets Sulfadiazine 0.5 Gm

SHARP & DOHME, INC.

Tablets Sulfadiazine 0.5 Gm

CANNOLL DUNHAM SMITH PHARMACEUTICAL CO.

Sulfadiazine Tablets 0.5 Gm

SMITH DORSEY COMPANY

Tablets Sulfadiazine 0.1 Gm and 0.5 Gm

E. R. SQUIBB & SONS

Sulfadiazine (*Powder*) 124.4 Gm and 497.6 Gm packages

Sulfadiazine Powder (Sterilized) 5 Gm vial

Tablets Sulfadiazine 0.5 Gm

THE UPJOHN COMPANY

Tablets Sulfadiazine 0.5 Gm

VOGEL LABORATORIES

Emulsion Sulfadiazine 5%, Sterilized 50 cc and 200 cc bottles. A 5 per cent suspension of sulfadiazine in an emulsion of beeswax, liquid petrolatum, triethanolamine and water.

WILLIAM R. WARNER & CO., INC.

Tablets Sulfadiazine 0.5 Gm

WINTHROP CHEMICAL COMPANY, INC.

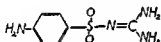
Tablets Sulfadiazine 0.5 Gm

WYETH INCORPORATED

Tablets Sulfadiazine 0.5 Gm

— U S P —

Sulfaguanidine has the following structural formula



For description and standards see First Bound Supplement U. S. Pharmacopeia XII under Sulfaguanidum and Tabellae Sulfaguanidini.

Clinical Pharmacology—The development of sulfaguanidine represented a new concept in bacterial chemotherapy, namely that a sulfonamide drug could be given by mouth and be quite soluble in the intestinal contents while at the same time it would be poorly absorbed from the gastrointestinal tract, thus permitting the drug to exert its bacteriostatic and bactericidal action locally in the gastrointestinal tract.

The proper use of this drug demands that the physician shall use optimal doses spaced at such intervals as will give rise to high concentration of the drug in the stool with possibilities for minimal absorption from the gastrointestinal tract. In actual practice one finds that when the drug is properly administered the concentrations of sulfaguanidine in the blood rarely exceed 5 mg. per hundred cubic centimeters.

On the basis of recent investigations the Council recognizes claims for the prophylactic use of sulfaguanidine as well as other sulfonamides in dysentery

Toxicity—Sulfaguanidine is the least toxic of all commonly used sulfonamide drugs but nausea with vomiting drug rash drug fever and other types of idiosyncrasy are not uncommon. If toxic reactions occur, the drug should be stopped and fluids forced and enemas given to eliminate the drug from the body as soon as possible

Dosage—In bacillary dysentery the initial dose by mouth is 0.05 Gm per kilogram of body weight followed by a maintenance dose of 0.05 Gm per kilogram every four hours day and night until the number of stools is five or less daily, then 0.05 Gm per kilogram every eight hours for at least 3 days. If improvement does not occur within seven days it is unlikely that the drug will be effective on further administration. It is generally not considered wise to continue the drug for a period of more than fourteen days

Preoperative and Postoperative Use in Colonic Surgery—When sulfaguanidine is being used as a prophylactic agent prior to operations on the colon the recommended dosage is 0.05 Gm per kilogram of body weight by mouth every eight hours day and night for five days before the operation. Then as soon as possible after the operation the drug should be started by mouth in the same dosage and continued for seven days. It is not as a rule necessary to continue the drug longer. It is recommended that the total period of dosage should not exceed fourteen days

LEDGERLE LABORATORIES, INC

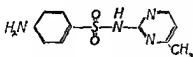
Sulfaguanidine (*Powder*) bulk
Tablets Sulfaguanidine 0.5 Gm

E. R. SQUIBB & SONS

Sulfaguanidine (*Powder*) 120 Gm and 453 Gm bottles
Tablets Sulfaguanidine 0.5 Gm

Sulfamerazine has the following structural formula

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Actions and Uses—The oral administration of equal doses of sulfamerazine and sulfadiazine produces in the blood a greater sulfonamide concentration of sulfamerazine than of sulfadiazine. In fact comparable blood concentrations are obtained with approximately one half the amount of sulfamerazine as is required of sulfadiazine. Sulfamerazine is more rapidly and more completely absorbed from the gastrointestinal tract but is excreted more slowly than sulfadiazine. Thus it may be given in smaller amounts and less frequently. This drug penetrates cerebrospinal pleura and peritoneal fluids; the concentration of free drug in cerebrospinal fluid is approximately 50 per cent of that in serum.

The acetylated form of sulfamerazine is more soluble in urine at pH 7 or less than either the free or acetylated forms of sulfadiazine and free sulfamerazine is more soluble than sulfadiazine in neutral or acid urine. The formation of drug concretions and renal parenchymal injury seems to be less likely to occur with sulfamerazine than with sulfadiazine if equal blood concentrations of the drug are maintained. Animal experiments suggest that the two drugs otherwise have about the same degree of toxicity but further clinical investigations in humans remain to be done to reveal the true toxicity status of sulfamerazine.

Sulfamerazine may be used in the treatment of pneumococcal streptococcal meningococcal and gonococcal infections.

Dosage—In the treatment of acute pneumococcal streptococcal and meningococcal infections the maintenance of a concentration of sulfamerazine in the blood of 10 to 15 mg of the drug per 100 cc of blood will usually be sufficient. Blood serum concentrations of this magnitude may be attained within four hours by the oral administration of 3 or 4 Gm of sulfamerazine as an initial dose followed by 10 Gm every eight hours. This dosage should be continued for seventy two hours after the temperature pulse and respiration rates return to normal.

For infants under six months of age 0.5 Gm initial dose and 0.25 Gm every twelve hours thereafter; infants six months to three years 1.0 Gm initial dose and 0.5 Gm every twelve hours; children three to ten years 1.5 Gm initial dose and 1.0 Gm every twelve hours. In very severe infections the dosage may be increased by 50 per cent.

In the treatment of pneumococcal infections type specific antiserum may be administered unless contraindicated if the response of the patient to the drug alone is not adequate within 18 to 24 hours.

As in the case of the other sulfonamides the appearance of toxic symptoms should be an indication for extreme caution in further therapy perhaps the cessation of all treatment with this drug.

Tests and Standards—

slightly soluble in ethyl alcohol and sparingly soluble in acetone. The melting point of sulfamerazine is 235-238 C.

Place about 0.5 Gm. of sulfamerazine in a test tube, wrap the upper portion of the test tube with wet filter paper and heat in a bath at 220-240 C. a white crystalline sublimate forms in the neck of the tube. The fumes evolved are those of ammonia. The residue appears as a white sulfapyridine.

Sulfathiazole produces a brown to red residue and odors of ammonia, aniline and hydrogen sulfide; sulfadiazine produces a reddish brown residue but no hydrogen sulfide or ammonia; sulfaguanidine produces a purple to violet residue and the odor of ammonia; sulfapyrazine produces a reddish brown residue and the odor of aniline. The crystalline sublimate has a characteristic 'mousy' odor and its melting point lies between 153 and 161 C. When recrystallized from hot benzene, the 2-amino-4-methylpyrimidine obtained melts sharply at 159-161 C. (distinction from other sulfonamide derivatives except sulfadiazine which gives a sublimate melting sharply at 126-127 C. when purified and sulfapyrazine which gives a sublimate melting sharply at 120-122 C.).

Dissolve about 0.1 Gm. of sulfamerazine in 0.5 cc. of tenth normal sodium hydroxide solution and dilute to 10 cc. with distilled water and add five drops of copper sulfate solution; an olive green precipitate forms which becomes purple gray on standing (distinction from sulfadiazine, which forms an olive green precipitate on standing from sulfapyridine, a precipitate that turns olive green, a precipitate from sulfaguanidine).

Sulfanilamide, which forms a pink precipitate in a slight pink one, from sulfapyrazine, which forms a green precipitate that turns white.

Dry an accurately weighed specimen of sulfamerazine at 100 C. for four hours; the loss in weight does not exceed 0.5 per cent.

Ignite about 1 Gm. of sulfamerazine accurately weighed. Cool and add sufficient sulfuric acid to moisten the charred mass and ignite to constant weight; the ash is not more than 0.1 per cent.

Digest 2.0 Gm. of sulfamerazine with 100 cc. of distilled water at about 70 C. for five minutes, cool and filter. (1) To 25 cc. of filtrate add two drops of phenolphthalein solution and titrate with tenth normal sodium hydroxide solution; not more than 0.5 cc. of the sodium hydroxide solution is required to produce a pink color. (2) To another 25 cc. of the filtrate add 1 cc. of nitric acid and 1 cc. of silver nitrate solution, mix well and add 1 cc. of 10 per cent sodium carbonate solution; the turbidity made with 0.1 cc. of 5 per cent barium chloride solution, mix well and allow to stand ten minutes; the turbidity does not exceed that produced in a control test made with 0.2 cc. of fiftieth normal sulfuric acid.

Dissolve 0.5 Gm. of sulfamerazine in a mixture of 5 cc. of sodium hydroxide solution and 20 cc. of distilled water; the solution is clear and not more than pale yellow in color; add five drops of freshly prepared 10 per cent sodium sulfide solution; the darkening produced does not exceed that developed in a control test to which has been added 0.01 mg. of lead.

Dissolve about 0.5 Gm. of dry sulfamerazine, accurately weighed, in 10 cc. of distilled water and 10 cc. of hydrochloric acid contained in a 250 cc. beaker, dilute to 50 cc., cool to 15 C. and titrate with tenth molar sodium nitrite solution. The endpoint is the first immediate blue.

streak obtained when a glass rod dipped into the solution is drawn across a smear of starch iodide paste on white filter paper (or clear glass plate). The solution should retain this endpoint for thirty seconds. Each cubic centimeter of tenth molar sodium nitrite corresponds to 0.02643 Gm of anhydrous sulfamerazine; the amount of sulfamerazine found corresponds to not less than 99.0 per cent nor more than 101.0 per cent.

LEDERLE LABORATORIES, INC

Sulfamerazine Powder (Unsterile) 114 and 454 Gm packages

Tablets Sulfamerazine, 0.25 Gm and 0.5 Gm

ELI LILLY & CO

Tablets Sulfamerazine 0.5 Gm

PARKE, DAVIS & CO

Tablets Sulfamerazine 0.5 Gm

SHARP & DOHME, INC

Sulfamerazine bulk, 114 Gm (unsterile)

Sulfamerazine Chemical Reagent (powder) 1 Gm vial

Tablets Sulfamerazine 0.5 Gm

E. R. SQUIBB & SONS

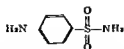
Tablets Sulfamerazine 0.5 Gm and 0.25 Gm

THE UPJOHN COMPANY

Tablets Sulfamerazine 0.5 Gm

SULFANILAMIDE

$\text{NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2$ —The
at 100°C for 4 hours
 $\text{C}_6\text{H}_5\text{O}_2\text{N}_2\text{S}$ "U S P"
tural formula



For description and standards see the U S Pharmacopoeia under Sulfanilamide and Sulfanilamide Tablets

Clinical Pharmacology—Sulfanilamide when administered by mouth is readily absorbed from the gastrointestinal tract. It is probable that, following a single peroral dose, absorption is practically complete within four hours. The drug is evenly distributed in all body tissues with the exception of the brain,

fat and bone. In patients with normal renal function, from 10 to 20 per cent of the circulating sulfanilamide is present in the acetylated or conjugated form. The drug is almost totally absorbed and is readily excreted by the normal kidneys. In the urine ordinarily from one third to one half of the excreted sulfanilamide exists as the acetylated fraction.

Toxicity.—No patient should be treated with sulfanilamide unless arrangements are made for daily attention by a physician. This is necessary because of the serious toxic effects of this drug, which, while not frequent, are generally unpredictable in their occurrence and probably result from an idiosyncrasy to sulfanilamide. Many patients receiving sulfanilamide will have signs and symptoms of central nervous system disturbances such as headache, dizziness, nausea, vomiting, mild depressions or clations and in a few instances, severe toxic psychoses. Because of these toxic manifestations, patients who are receiving the drug should be warned against driving automobiles, piloting or riding in airplanes and doing any heavy or dangerous work in which a spell of dizziness might result in a serious accident. Practically all individuals who receive therapeutic doses of the drug develop some degree of cyanosis, generally apparent in the lips and nail beds, but in some cases suffusing the entire integument. The exact mode of production of this cyanosis is unknown, although in many instances it is due, at least in part, to the production of methemoglobin in the blood. It is not, in the opinion of most observers, a serious complication and rarely serves as an indication that treatment should be discontinued. Drug fever, which commonly occurs between the fifth and ninth days of therapy, is a not infrequent toxic manifestation. Rashes, which may vary in their type and which may be accompanied by fever, are also not infrequently seen in the course of sulfanilamide therapy. As these rashes are sometimes the result of a photosensitization of the skin, it is probably best for patients who are receiving sulfanilamide to keep out of the sun, and they should not receive ultraviolet irradiation.

Acidosis may be produced by the drug in certain individuals. This is probably brought about by the action of sulfanilamide in inhibiting the enzyme carbonic anhydrase. The routine, concurrent use of sodium bicarbonate generally prevents this complication of drug therapy. Hepatitis, accompanied by jaundice and, in a few instances, ending fatally, is one of the rarer complications of sulfanilamide therapy. Acute hemolytic anemia occurring from the first to the twenty first day of therapy, is not uncommon and is noted more frequently in Negro patients than in white patients. A severe leukopenia may occur at any time during the course of therapy, and granulocytopenia has been described not uncommonly as a toxic manifestation. The most common time for the appearance of true agranulocytosis is between the fourteenth and fortieth days of therapy.

During this period white blood cell counts should be done at least every two days. In patients who have a decrease in renal function the normal excretion of the drug is impaired and an accumulation of sulfanilamide in the blood and tissues of the patient may occur if care is not taken in regulating the dosage of the drug.

As far as is known practically all other drugs may be prescribed concurrently (but not in combination) with sulfanilamide.

Dosage—The dose of sulfanilamide depends on the type and severity of the infection. It is suggested that in cases of serious infection an initial peroral dose of 0.1 Gm per kilogram of body weight be administered this to be followed by doses of the drug of one sixth the amount of the initial dose given at four hour intervals day and night until the temperature has been normal for seventy-two hours. Then the dose of the drug may be gradually decreased until complete convalescence is established. It is to be remembered that the main index for the control of therapy with this drug should not be the dose of the drug which has been prescribed but rather the concentrations of sulfanilamide that are being obtained in the blood or other tissue fluids. It is usually advisable to continue therapy for a few days after clinical recovery has taken place in order to avoid relapses. Patients who cannot take the drug by mouth may be given subcutaneous injections of a 1 per cent solution of sulfanilamide made up in isotonic solutions of sodium chloride or better still in one sixth molar sodium racemic lactate solutions. The same total dosage may be employed for parenteral as for oral administration but the injections should be given at intervals of from six to eight hours.

ABBOTT LABORATORIES

Sulfanilamide (*Crystals*) 10 Gm and 40 Gm ampuls

Tablets Sulfanilamide 0.324 Gm and 0.5 Gm

AMERICAN PHARMACEUTICAL CO. INC.

Sulfanilamide (*Powder*) 28.35 Gm 113.4 Gm and 453.6 Gm packages

Tablets Sulfanilamide 0.324 Gm and 0.486 Gm

GEORGE A. BREON & COMPANY INC.

Tablets Sulfanilamide 0.324 Gm

CIBA PHARMACEUTICAL PRODUCTS INC.

Tablets Sulfanilamide 0.5 Gm

THE DRUG PRODUCTS CO., INC.

Pulvoids Sulfanilamide: 0.324 Gm

ENDO PRODUCTS, INC.

Tablets Sulfanilamide: 0.324 Gm and 0.5 Gm

FLINT, EATON & COMPANY

Tablets Sulfanilamide: 65 mg, 0.324 Gm and 0.5 Gm

GANE AND INGRAM, INC.

Sulfanilamide (*Powder*): bulk

CHARLES C. HASKELL & Co., INC.

Tablets Sulfanilamide: 0.324 Gm

HORTON & CONVERSE

Tablets Sulfanilamide: 0.324 Gm

HYNSON, WESTCOTT & DUNNING, INC.

Sulfanilamide (Sterile Crystalline): 5 gram shaker-type package

LEDERLE LABORATORIES, INC.

Sulfanilamide (*Powder*): 120 Gm and 453 Gm packages

Sulfanilamide Surgical Powder (Sterile): 5 Gm puffer tube

Tablets Sulfanilamide: 0.324 Gm

ELI LILLY AND COMPANY

Sulfanilamide (*Powder*): bulk

Pulvules Sulfanilamide: 0.13 Gm and 0.324 Gm

McNEIL LABORATORIES, INC.

Tablets Sulfanilamide: 0.162 Gm, 0.324 Gm and 0.5 Gm

MALLINCKRODT CHEMICAL WORKS

Sulfanilamide (*Powder*): bulk

THE MALTBE CHEMICAL COMPANY

Tablets Sulfanilamide: 0.324 Gm

MERCK & Co., INC.

Sulfanilamide (*Powder*): bulk

THE WM S MERRELL COMPANY

Tablets Sulfanilamide 0.324 Gm and 0.5 Gm

E S MILLER LABORATORIES, INC

Tablets Sulfanilamide 0.324 Gm

NATIONAL DRUG COMPANY

Sulfanilamide (*Powder*) 453 Gm

Tablets Sulfanilamide 65 mg 0.324 Gm and 0.5 Gm

PARKE DAVIS & COMPANY

Tablets Sulfanilamide 0.324 Gm and 0.5 Gm

PITMAN MOORE COMPANY

Tablets Sulfanilamide 0.324 Gm

SCHIEFFELIN & CO

Tablets Sulfanilamide 0.324 Gm and 0.5 Gm

SHARP & DOHME INC

Tablets Sulfanilamide 0.324 Gm and 0.5 Gm

CARROLL DUNHAM SMITH PHARMACAL CO

Tablets Sulfanilamide 0.324 Gm

SMITH DORSEY COMPANY

Tablets Sulfanilamide 0.162 Gm 0.324 Gm and 0.5 Gm

Sulfanilamide (*Powder*) 5 Gm vials

E R SQUIBB & SONS

Sulfanilamide (*Powder*) 120 Gm and 453 Gm bottlesSulfanilamide (*Crystals*) 1 Gm ampuls

Tablets Sulfanilamide 0.324 Gm and 0.5 Gm

FREDERICK STEARNS & COMPANY DIVISION

Tablets Sulfanilamide 0.3 Gm

THE UPJOHN COMPANY

Tablets Sulfanilamide 65 mg 0.324 Gm and 0.5 Gm

WILLIAM R WARNER & CO., INC

Tablets Sulfanilamide 0.32 Gm

WARREN TEED PRODUCTS COMPANY

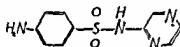
Tablets Sulfanilamide 0.33 Gm

WILEY, INCORPORATED

Tablets Sulfanilamide 0.324 Gm and 0.5 Gm

SULFAPYRAZINE.—2 Sulfanilamidopyrazine—2 Sulfanilaminopyrazine—*p*-Amino N 2 pyrazinylbenzenesulfonamide— $C_{12}H_{10}N_4O_2S$ (MW 250.27)

Sulfapyrazine has the following structural formula



Actions and Uses—Sulfapyrazine appears to have a low order of toxicity in experimental animals. Although renal damage has been shown in adults this reaction is not unlike that caused by other sulfonamides. Other reactions may be blood dyscrasias, drug fever, rash, nausea and vomiting (although this occurs less frequently than with other sulfonamides). Because the substance is absorbed and excreted rather slowly, high blood levels are not obtained with single large oral doses. Dosages of one gram every four or six hours will provide adequate levels with this concentration remaining fairly constant over considerable periods of time. The drug is secreted in the cerebrospinal fluid and reaches concentrations of about one half to two thirds of blood level within 12 hours following intravenous administration of sulfapyrazine sodium. It is secreted also in other body fluids. It has a low degree of conjugation to acetyl sulfapyrazine.

Sulfapyrazine is probably as effective as sulfadiazine in the treatment of pneumococcal, hemolytic streptococcal and B. coli infections. Further it appears to be effective against *Shigella paradysenteriae* even when these strains are resistant to other sulfonamides and in the presence of meningococcal meningitis.

Dosage—Low blood levels commonly follow administration of sulfapyrazine and often are effective. The usual dosage however produces concentrations from 5 to 12 mg per 100 cc of blood.

Initial dose for adults is 2 to 4 grams followed by 1 gram doses at four to six hour intervals. Treatment should be continued until the temperature, pulse and respiration have been normal for three days. Infants and children should receive about 130 mg of the drug per kilo of body weight. In general infants under six months of age may receive 0.5 Gm as an initial dose and 0.25 Gm every six hours thereafter. Children

six months to three years, 10 gram initial dose 0.5 Gm every six hours, children three to ten years 20 Gm initial dose and 10 Gm every six hours. In very severe infections the dose may be increased by 50 per cent.

If adequate response to the drug is not obtained within 24 hours, type specific serum should be given unless contraindicated.

Tests and Standards—

Sulfapyrazine occurs as an odorless tasteless white or yellowish

hydroxide and dilute to 10 cc with distilled water. Add five drops of copper sulfate solution. A light pea green precipitate forms which becomes white on standing (distinction from sulfapyridine which forms an apple green precipitate that turns olive green from sulfadiazine which forms an olive green precipitate changing to purple gray on standing from sulfanilazine which gives an olive green precipitate changing to dark gray on standing from sulfathiazole which forms a violet precipitate from sulfanagazine which forms a dark brown precipitate and from sulfanilamide which forms no precipitate or a light blue one).

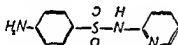
Dissolve 0.5 Gm. of sodium hydroxide solution in 10 cc. of distilled water and not more than 10 cc. of freshly prepared 10 per cent sodium nitrite solution. The solution should not exceed that developed in a control test to which has been added 0.01 mg. of lead.

Dissolve about 0.5 Gm. of sulfapyrazine in 10 cc. of distilled water and 10 cc. of hydrochloric acid contained in a 250 cc. beaker, dilute to 50 cc., cool to 15 C., and titrate with tenth molar sodium nitrite solution. The endpoint is the first immediate blue streak obtained when a glass rod dipped into the solution is drawn across a smear of starch iodide paste on white filter paper (or clear glass plate). The solution should retain this endpoint for 30 seconds. Each cubic centimeter of tenth molar sodium nitrite corresponds to 0.02503 Gm. of anhydrous sulfapyrazine; the amount of sulfapyrazine found corresponds to not less than 99.0 per cent nor more than 101.0 per cent.

MEAD JOHNSON & COMPANY

Tablets Sulfapyrazine: 0.5 Gm.

SULFAPYRIDINE—"When dried at 100° C. for 4 hours, contains not less than 99 per cent of $C_{11}H_{11}N_2O_2S$ " U. S. P.



For description and standards see the U. S. Pharmacopeia under Sulfapyridine and Sulfapyridine Tablets.

Clinical Pharmacology—In comparison with sulfanilamide, sulfapyridine is irregularly and often poorly absorbed. These differences in absorption seem to be due to an individual response on the part of the patient. The drug is, as a rule, conjugated to a higher degree than is sulfanilamide. The degree of conjugation is desirable in the treatment of certain diseases. In its absorption and conjugation may make treatment with it more difficult than when sulfanilamide is used. As far as is known, that fraction of the drug which is absorbed is excreted mainly by the kidneys in the free and conjugated forms. As a rule, the drug is conjugated to the acetylated form in the urine to a higher degree than is sulfanilamide. Excretion of sulfapyridine is slower than is that of sulfanilamide, and it may be four or five days after the drug has been stopped before it is entirely eliminated from the body.

No patient should be treated with sulfapyridine unless arrangements have been made for daily attention by a physician. If the patient is suffering from lobar or bronchial pneumonia, every effort should be made to ascertain (by bacteriologic examination of the sputum obtained before drug treatment is begun) the etiologic agent which is causing the pneumonia, and,

if it is a pneumococcus to type the organism in order that serum may be given if the pneumonia proves resistant to sulfapyridine therapy

Toxicity—The toxic manifestations of sulfapyridine therapy are essentially those previously noted in the course of sulfanilamide therapy and while in general the occurrence of toxic manifestations are not as frequent when sulfapyridine is used they may be very severe. The toxic effects of this drug are unpredictable in their occurrence and presumably have as their basis an idiosyncrasy. Nausea and vomiting sometimes

ment and severe leukopenia or even granulocytopenia is not uncommon. It has been noted that children who are receiving sulfapyridine are more likely to develop a severe leukopenia than is the case when sulfanilamide is being given. Serious instances of hepatitis have been reported. Instances of gross hematuria with and without signs of renal failure have been noted in patients receiving this drug. It is likely that the hematuria is associated with the formation of acetylsulfapyridine deposits in the renal tubules and pelves although the possibility of a direct toxic action on the kidney has not yet been ruled out. Because it is known that acetylsulfapyridine crystals are frequently found in the urine of patients who are receiving sulfapyridine it is wise to administer enough fluid to keep their urinary output at a normal level (1000 cc) in order to lessen the possible chances of calculus formation. If severe toxic manifestations of drug therapy arise sulfapyridine should be stopped and fluids forced in order that it may be eliminated from the body as quickly as possible.

As far as is known, sulfapyridine can be used concurrently with any other drugs.

Dosage—In adults suffering from lobar pneumonia large initial doses such as 4 Gm are given in a single dose followed by 1 Gm of the drug every four hours by mouth this to be continued until the temperature has been normal for at least seventy two hours. Concentrations of 4 to 6 mg of free sulfapyridine for each hundred cubic centimeters of blood seem to be necessary for prompt therapeutic responses to the drug. In infants and children the initial dose is 0.06 Gm per pound up to 40 pounds (18 Kg) of body weight, larger children require slightly less in proportion to their weight hence a total of 40

grains (2.6 Gm) is sufficient for a child weighing not more than 50 pounds (23 Kg) a limit of not more than 3 Gm to be given to any child weighing less than 60 pounds (27 Kg). The total daily dose is calculated in the same manner, is divided into four parts and given at six hour intervals until the temperature has been normal for thirty six hours. The drug may be stopped earlier in children than in adults without danger of relapse.

In the treatment of gonococcic infections in adults the following dosage schedule has been shown to give good results: the first day 3 Gm then 2 Gm a day for the succeeding nine days.

AMERICAN PHARMACEUTICAL CO. INC.

Tablets Sulfapyridine 0.5 Gm

CIBA PHARMACEUTICAL PRODUCTS INC.

Tablets Sulfapyridine 0.5 Gm

ENDO PRODUCTS INC.

Tablets Sulfapyridine 0.5 Gm

FLINT EATON & COMPANY

Tablets Sulfapyridine 0.5 Gm

LEDERLE LABORATORIES INC.

Tablets Sulfapyridine 0.5 Gm

ELI LILLY AND COMPANY

Tablets Sulfapyridine 65 mg 0.5 Gm and 0.25 Gm

MERCK & CO. INC.

Sulfapyridine (Powder)

Tablets Sulfapyridine 0.5 Gm

NATIONAL DRUG COMPANY

Tablets Sulfapyridine 0.5 Gm

PARKE DAVIS & COMPANY

Capsules Sulfapyridine 0.25 Gm

Tablets Sulfapyridine 0.5 Gm

PITMAN MOORE COMPANY

Tablets Sulfapyridine 0.5 Gm

CARROLL DUNHAM SMITH PHARMACEUTICAL CO.

Tablets Sulfapyridine 0.5 Gm

SMITH DORSEY COMPANY

Tablets Sulfapyridine 0.5 Gm

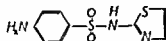
FREDERICK STEARNS & COMPANY DIVISION

Tablets Sulfapyridine 0.5 Gm

WYETH INCORPORATED

Tablets Sulfapyridine 0.5 Gm

SULFATHIAZOLE—“When dried at 100° C. for 4 hours contains not less than 99 per cent of $C_8H_7N_3O_2S_2$.”
 U S P Sulfathiazole has the following structural formula



It may be prepared by the condensation of p acetylamino benzenesulfonylchloride with 2 aminothiazole in pyridine. The compound 2(p acetylamino benzenesulfonamido) thiazole separates on dilution of the reaction mixture with water and is subsequently hydrolyzed with hydrochloric acid. Sulfathiazole is then isolated by neutralization of the acid solution to Congo red and purified by recrystallization from alcohol.

For description and standards see the U S Pharmacopeia under Sulfathiazole and Sulfathiazole Tablets.

Clinical Pharmacology—Sulfathiazole resembles sulfanilamide in certain of its pharmacologic effects. In most patients it is rapidly absorbed when administered by mouth, maximum concentrations of the drug in the blood being obtained in three to six hours after the administration of a single dose. It is fairly evenly distributed throughout most of the body tissues with the exception that it does not pass readily into the spinal fluid. In the tissues a certain proportion of the drug is conjugated to the therapeutically inactive acetyl derivative. The degree of conjugation is as a rule slightly greater than that noted for sulfanilamide but generally less than that for sulfapyridine. It is excreted rapidly by the kidneys and because of this it is sometimes difficult to maintain adequate concentrations of the drug in the blood and tissues. The rapid excretion of this drug is probably responsible for its relatively low degree of conjugation. If kidney function is impaired the excretion of sulfathiazole will be reduced and the drug will accumulate in the blood and tissues.

In the urine considerably less sulfathiazole is found in the conjugated form than has been generally noted for either sulfanilamide or sulfapyridine. The excretion of the drug is generally almost complete within twenty-four hours after the administration of a single dose of the compound.

Toxicity.—The toxic manifestations noted in the course of sulfathiazole therapy are similar to those previously noted in the course of therapy with sulfanamide or sulfapyridine. These untoward effects are more frequent in their occurrence and are considered to be the result of an idiosyncrasy to the drug.

Patients who are receiving this drug should be seen daily by their physicians in order that any possible toxic effects arising in the course of the administration of sulfathiazole may be noted and appropriate steps taken to eliminate the drug.

Sulfathiazole causes less nausea, vomiting and diarrhea than does sulfapyridine. Mental disturbances of such nature are uncommon. Quincke's so-called peripheral neuritis has been reported occasionally but generally mild if present, and seldom of long duration. Sulfathiazole produces more instances of drug fever and drug rash than any of the other sulfonamide compounds in common use. These toxic manifestations generally occur between the fifth and ninth days of treatment but may occur at any period. Urthral or nodal rashes resembling erythema nodosum are often seen. Patients receiving the drug should be kept out of the sun.

Hepatitis is rare. Leukopenia with granulocytopenia has been noted either early or late in the course of therapy. Acute agranulocytosis has been reported as occurring in course of therapy with this drug. Mild to severe acute hemolytic anemia are uncommonly seen. Micro, or gross hematuria has occurred in patients who have received this drug and anemia with at least a has been observed. The hematuria and more severe evidence of kidney damage may be due in certain instances to the formation of acetylsulfathiazole crystals and renal calculi which block the renal tubules or even the renal pelvis and ureters, but in other patients these toxic manifestations seem to result from a direct toxic reaction of the drug on the renal epithelium. Because of these renal toxic reactions it is important to keep the urinary output at not less than 1000 cc. in the course of therapy with sulfathiazole.

A curious toxic manifestation which has not been reported in the course of therapy with sulfanilamide or sulfapyridine and which has been reported only in the course of sulfathiazole therapy, is the injection of the scleras and conjunctivas which when severe may give the appearance of the disease "pink eye." Mild to severe arthralgia may accompany the fever and rashes which are produced by sulfathiazole.

When fever, rash, hepatitis, granulocytopenia, acute hemolytic anemia, hematuria with oliguria, injection of the scleras and conjunctivas or other serious toxic manifestations occur, the drug should be stopped and fluids forced in order that sulfathiazole may be eliminated from the body as rapidly as possible.

As far as is known at the present time, sulfathiazole can be used concurrently with any other drugs.

Dosage.—Sulfathiazole is poorly soluble and hence must be administered by the oral route. In the treatment of pneumo-

coccic pneumonia in adults the initial dose of sulfathiazole should be 4 Gm., to be followed by 1 Gm. every four hours day and night until the patient's temperature has been normal for seventy-two hours. The drug should then be discontinued. In children ill with pneumococcic pneumonia the initial dose should be based on 0.15 Gm. per kilogram (up to 25 Kg. of body weight) and the total daily dose is calculated on the same basis. The total daily dose should be divided into four equal parts and administered at six hour intervals until the temperature has been normal for thirty-six hours. The drug should then be stopped.

It is to be remembered that surgical measures, both supportive and operative must be used in the treatment of staphylococcic infections in conjunction with sulfathiazole whenever indicated. Surgical drainage of purulent foci is generally advised because, while the drug may halt the invasive manifestations of staphylococcic infection, it may not by itself cure areas of localized infections, and a flare up of the infection from such areas may occur if they are not properly drained.

The drug should not be used for the peroral treatment of minor staphylococcic infections such as localized boils and small carbuncles or any mild furunculosis. In large boils or carbuncles the initial dose for adults should be 4 Gm., followed by 1 Gm. every four hours day and night from five to seven days. In diffuse staphylococcic cellulitis lymphangitis or acute osteomyelitis in adults 4 Gm. should be given as an initial dose, to be followed by doses of 1.5 Gm. every four hours day and night as long as evidence of a spreading infection continues. The dose should then be reduced to 1 Gm. every four hours day and night and continued as indicated. In staphylococcic bacteremia the initial dose for adults should be 4 Gm. followed by 1.5 Gm. every four hours day and night until the temperature has been normal for forty-eight hours. The dose may then be reduced to 1 Gm. to be given every four hours day and night for fourteen days at which time the dose may be reduced to 0.5 Gm. every four hours day and night to be continued for a minimum of fourteen days. In severe staphylococcic infection in children the initial dose should be calculated on the basis of 0.2 Gm. per kilogram of body weight (up to 20 Kg. of weight). The total daily dose is calculated on the same basis and should be divided into six parts, given at four hour intervals day and night until the temperature has been normal for forty-eight hours. The dose may then be reduced to 1 Gm., to be given every four hours day and night for fourteen days, at which time the dose may be reduced to 0.5 Gm. every four hours day and night to be continued for a minimum of fourteen days. In staphylococcic bacteremia there is a great possibility that a relapse will occur unless prolonged treatment with the drug is employed. Sulfathiazole is at the present time the drug of choice in the treatment of gonorrhea. When used in this infection the first day's dose is 3 Gm., and 2 Gm. should be administered for

the following nine days. If at the end of five days a pronounced improvement has not been noted a shift should be made to either sulfapyridine or sulfadiazine.

It is very important to control the administration of sulfathiazole by determining its concentration in the blood of patients who are receiving it. In pneumonia concentrations of from 4 to 6 mg. per hundred cubic centimeters of the drug in the blood should be sought.

ABBOTT LABORATORIES

Tablets Sulfathiazole 0.25 Gm. and 0.5 Gm.

AMERICAN PHARMACEUTICAL CO. INC.

Tablets Sulfathiazole 0.5 Gm.

GRACE A. BRON & COMPANY, INC.

Tablets Sulfathiazole 0.5 Gm.

BUTRINGTON'S, INC.

Tablets Sulfathiazole 0.5 Gm. and 0.25 Gm.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Sulfathiazole (*Powder*) 5 Gm. bottle

Sulfathiazole Tablets 0.5 Gm.

THE DRUG PRODUCTS CO., INC.

Pulvoids Sulfathiazole 0.5 Gm.

ENDO PRODUCTS, INC.

Tablets Sulfathiazole 0.5 Gm.

JOINT PATON & COMPANY

Tablets Sulfathiazole 0.5 Gm.

LEDERLE LABORATORIES, INC.

Sulfathiazole (*Powder*) 120 Gm. and 453 Gm. packages

Sulfathiazole Surgical Powder (Sterile) 5 Gm.

Tablets Sulfathiazole 0.5 Gm.

ELI LILLY AND COMPANY

Sulfathiazole (*Powder*) Bulk

Tablets Sulfathiazole 65 mg., 0.25 Gm. and 0.5 Gm.

MCFIL LABORATORIES, INC.

Tablets Sulfathiazole: 05 Gm

THE MAITHE CHEMICAL COMPANY

Sulfathiazole (*Powder*): 30 Gm vial

Tablets Sulfathiazole: 05 Gm

MERCK & Co., INC.

Sulfathiazole (*Powder*).

Tablets Sulfathiazole: 05 Gm

THE WM. S. MERRELL COMPANY

Tablets Sulfathiazole: 05 Gm

E. S. MILLER LABORATORIES, INC.

Tablets Sulfathiazole: 05 Gm

PARKE, DAVIS & COMPANY

Tablets Sulfathiazole: 0.25 Gm and 0.5 Gm

PITMAN-MOORE COMPANY

Tablets Sulfathiazole: 0.25 Gm (children's) and 0.5 Gm

PRIMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Sulfathiazole: 05 Gm

SCHIFFLIN & Co.

Tablets Sulfathiazole: 05 Gm

SHARP & DOHME, INC.

Tablets Sulfathiazole: 05 Gm

CARROLL DUNHAM SMITH PHARMACEUTICAL CO.

Tablets Sulfathiazole: 05 Gm

SMITH-DOOLEY COMPANY

Tablets Sulfathiazole: 05 Gm

Sulfathiazole (*Powder*): 5 Gm vials

L. R. SQUINN & SONS

Sulfathiazole (*Powder*): 5 Gm vial

Sulfathiazole Powder Sterilized: 5 Gm vials

Tablets Sulfathiazole: 05 Gm

FREDERICK STEARNS & COMPANY DIVISION

Tablets Sulfathiazole 05 Gm

THE UPJOHN COMPANY

Tablets Sulfathiazole 0.25 Gm and 0.5 Gm.

VOGEL LABORATORIES

Emulsion Sulfathiazole 5%, Sterilized 50 cc. and 200 cc. bottles A 5 per cent suspension of sulfathiazole in an emulsion of beeswax liquid petrolatum triethanolamine and water For topical use

Emulsion Sulfathiazole 10%, Sterilized 50 cc. and 200 cc. bottles A 10 per cent suspension of sulfathiazole in an emulsion of beeswax liquid petrolatum triethanolamine and water For topical use

WILLIAM R. WARNER & CO., INC.

Tablets Sulfathiazole 05 Gm

WARREN-TEED PRODUCTS COMPANY

Tablets Sulfathiazole 05 Gm

WINTHROP CHEMICAL COMPANY, INC.

Tablets Sulfathiazole 0.25 Gm and 0.5 Gm.

WYETH INCORPORATED

Tablets Sulfathiazole 05 Gm

SUCCINYLSULFATHIAZOLE — 2 (N⁴ succinylsulfanilamido) thiazole monohydrate — 2 (p succinylaminobenzene sulfonamido) thiazole monohydrate — $C_{22}H_{23}N_3O_6S_2 \cdot H_2O$ — M W 373.4 When dried at 100° C for 6 hours contains not less than 99 per cent of $C_{22}H_{23}N_3O_6S_2$ — *U S P*

Succinylsulfathiazole possesses the following structural formula



For description and standards see First Bound Supplement Pharmacopeia XII under Succinylsulfathiazole and Succinyl sulfathiazole Tablets

Actions and Uses—While succinylsulfathiazole has some resemblance to sulfathiazole animal experiments show it to have low toxicity and to be poorly absorbed from the intestinal

tract. Thus it has been proposed for use as an intestinal bacteriostatic agent particularly with reference to gram negative organisms. Succinylsulfathiazole while used in the intestinal tract for its local bacteriostatic effect appears to differ from sulfaguanidine in toxicity—succinylsulfathiazole being less toxic. It has been proposed for use in preoperative preparation and postoperative treatment of patients requiring surgical procedure on the intestinal tract such as operations for ulcerative carcinoma of the rectum carcinoma of the colon fecal fistulae ileostomy tumor of the cecum etc. It is valuable in the treatment of acute bacillary dysentery and of carriers of dysentery bacilli. It also may be used for prophylaxis of dysentery.

Dosage—Preoperative initially 0.25 Gm per kilo of body weight by mouth followed by a maintenance dose of 0.25 Gm per kilo daily in six equal portions at four hour intervals. Postoperative 0.25 Gm per kilo daily for one or two weeks depending on the postoperative condition. Postoperative administration should be begun as soon as the patient can take an ounce of water without undue nausea.

SHARP & DOHME INC

Sulfasuxidine (Powder) 115 Gm and 450 Gm glass jars

Tablets Sulfasuxidine 0.5 Gm

U S patents 2,324,013 and 2,324,014 (July 13, 1943 exp res 1960)
U S trademark No 394,111

Sulfonamide Sodium Salts

Clinical Pharmacology—Solutions of sulfonamide sodium salts in distilled water are strongly alkaline and have pH ranges of from 9 to 11. When solutions of these drugs are injected intravenously the sodium ions are promptly split off leaving the sulfonamide compound in the circulating blood. Hence in the final analysis sulfonamide sodium salts represent vehicles for introducing the slightly soluble parent compounds into the body. The preferred salts of sulfonamide compounds are 5 per cent solutions. The possibility that boiling result in the breakdown of the sodium salts it is considered unwise and even unnecessary to attempt to sterilize 5 per cent solutions of these salts which are going to be used for intravenous therapy.

The administration of 5 per cent solutions of the sodium salts of the sulfonamide compounds by the intravenous route should be carried out carefully because these solutions being highly alkaline are definitely irritating to the tissues and if they are permitted to leak outside the vein may cause necrosis of the tissues with sloughing. Solutions of such strength should never be given by the subcutaneous intramuscular or intrathecal route because of the danger of producing a chemical necrosis.

of the tissues. Recently it has been shown that 0.3 to 0.7 per cent solutions of the sodium salts of the sulfonamide compounds can be safely administered in saline or isotonic solution of three chlorides by the subcutaneous route. However, the general use of this route is not advised unless the drugs cannot be administered by the intravenous route.

Actions and Uses—The indications for the use of solutions of the sodium salts of sulfonamide compounds are those instances of severe infection in which it is desired to obtain promptly adequate blood concentrations of these drugs, or for patients who by reason of disturbances of the gastrointestinal tract, such as vomiting, are not obtaining proper concentrations of these drugs when they are given orally and, finally, for patients in whom the absorption of these drugs is poor or their rate of conjugation is such that adequate concentrations cannot be obtained in the blood and tissues by other routes of administration.

With the exception of patients ill with severe infections or those individuals to whom these drugs cannot be given by the oral route, it is rarely necessary to administer intravenous injections of solution of the sodium salts of the sulfonamides more than once or twice. Frequent and repeated injections of the drug are not generally advised, because such injections tend to produce thrombosis of the veins. Whenever possible, rather than continuing administration of solution of sodium salt of the sulfonamide compounds by the parenteral route, administration of the parent drug should be commenced by the oral route.

Toxicity—Aside from the damage to tissues which may result from the careless administration of the sodium salts of these sulfonamides by the intravenous route, the toxic reactions noted in the course of their administration are those which are noted when the parent sulfonamide is administered by the oral route.

SULFADIAZINE SODIUM—The sodium salt of 2-sulfanilamidopyrimidine— $C_{10}H_8N_4O_2S Na$ (M W 272.26). When dried at $105^\circ C$ for 4 hours, contains not less than 99 per cent of $C_{10}H_8N_4O_2S Na$.—U S P

For description and standards see First Bound Supplement U S Pharmacopeia XII under Sulfadiazine Sodium.

Actions and Uses—The sodium salt of sulfadiazine has the same therapeutic activities and properties as does sulfadiazine. This compound has proved to be of value in the treatment of severe hemolytic streptococcus, pneumococcus, meningococcus, staphylococcus and Escherichia coli tissue infections.

Dosage—The usual initial dose of this drug for patients severely ill with pneumonia is based on 0.06 Gm per kilogram of body weight, this being made up in a 5 per cent solution in sterile distilled water.

In severe staphylococcal, meningococcal or hemolytic streptococcus infections the initial dose should be 0.10 Gm per kilogram of body weight. It is also desirable to attempt to continue therapy by the oral route, but, if this is not possible, sodium sulfadiazine sodium should be used. The dose is 0.10 Gm per kilogram of body weight, made up in a 5 per cent solution in distilled water and administered by the intravenous route at about twelve to fifteen hour intervals. When solutions of sodium sulfadiazine are being used as the sole means of therapy, daily determinations of the concentration of the drug in the blood should be made in order to prevent inordinately high levels of the drug from accumulating in the blood.

LEDERLE LABORATORIES, INC

Solution Sodium Sulfadiazine 25% W/V 10 cc ampules
Each cubic centimeter contains sodium sulfadiazine 25 Gm in distilled water. Sodium thiosulfate 0.1 per cent used as preservative.

SHARP & DOHME, INC

Sterile Solution Sodium Sulfadiazine 5% W/V 50 cc ampules
Each 50 cubic centimeters contains sodium sulfadiazine 25 Gm and distilled water q. s.

E. R. SQUIBB & SONS

Sulfadiazine Sodium Powder (Nonsterilized) 50 Gm bottle

STERILE SULFADIAZINE SODIUM—Sterile Sodium Sulfadiazine—U. S. P. When dried at 105° C for 4 hours contains not less than 99 per cent of $C_{10}H_{10}N_4O_2SNa$ —U. S. P.

For description and standards see First Bound Supplement U. S. Pharmacopeia XII under Sterile Sulfadiazine Sodium.

Actions, Uses and Dosage—Same as for Sulfadiazine Sodium.

SHARP & DOHME, INC

Sodium Sulfadiazine (Sterile Powder) 5 Gm vials

E. R. SQUIBB & SONS

Sulfadiazine Sodium Powder (Sterilized) 5 Gm vial

SULFAMERAZINE SODIUM—The anhydrous sodium salt of 4-methyl-2-sulfanilamidopyrimidine— $C_{10}H_{10}N_4O_2SNa$ (M. W. 286.29).

Actions and Uses.—Sodium sulfamerazine may be used intravenously for critically ill patients who require immediate and adequate drug therapy, and for patients in whom it is difficult to obtain a satisfactory drug concentration with oral administration. However, oral administration should be begun with the intravenous administration, or immediately thereafter if possible. Intravenous treatment should be discontinued as soon as a satisfactory drug level can be maintained by oral administration.

Dosage.—The initial dose of sodium sulfamerazine is 0.05 Gm per kilogram of body weight, which should result in about 15 to 20 mg of free sulfamerazine per 100 cc of blood. This is administered as a 5 per cent solution in sterile distilled water. To maintain an effective level, 10 Gm every 6 or 8 hours may then be administered orally. If necessary, a second intravenous dose of 0.05 Gm per kilogram may be given twelve hours after the initial injection, provided the concentration of free and total sulfamerazine in the blood has first been determined.

Tests and Standards—

Sulfamerazine N N R
bitter tasting pow
freely soluble in
in ether, chlorofo
solutions of sulf
of a 5 per cent
dioxide to cause precipitation of sulfamerazine
Dissolve 2.0 Gm of " in 10 cc of water
add 10 cc of
filtrate meet the
Sulfamerazine N N R
at 100 C the
under Sulfame
sodium in 25 cc
pale yellow, and
Sulfamerazine N N R

Dry an accurately weighed portion of sulfamerazine sodium at 110 C. for four hours; the loss in weight is not more than 2.0 per cent. (Sulfamerazine sodium also occurs as a monohydrate with a moisture content of about 5.6 per cent.)
Sulfamerazine sodium accurately
Ignite until the ca
sulfuric acid heat
constant weight; the residue corresponds to tests for sodium and its weight corresponds to not less than 23.6 per cent nor more than 25.0 per cent.

Dissolve about 0.5 Gm of dry sulfamerazine sodium, accurately weighed, in 10 cc of distilled water and 20 cc of hydrochloric acid contained in a 250 cc beaker; dilute to 50 cc, cool to 15 C, and titrate with tenth molar sodium nitrite solution.

The endpoint is the first immediate blue streak obtained when a glass rod dipped into the solution is drawn across a smear of starch iodide-paste on white filter paper (or clear glass plate). The solution should retain this endpoint for thirty seconds. Each cubic centimeter of tenth molar sodium nitrite corresponds to 0.07863 Gm of anhydrous sulfamerazine sodium; the amount of sulfamerazine sodium found corresponds to not less than 99.0 per cent nor more than 101.0 per cent.

LEDERLE LABORATORIES, INC

Solution Sodium Sulfamerazine 25% W/V · 10 cc ampuls

SHARP & DOHME, INC

Sterilized Sodium Sulfamerazine 5 Gm vial

Sterile Solution Sodium Sulfamerazine 6% 50 cc ampules Each 50 cc contains sodium sulfamerazine 3 Gm in distilled water

SULFAPYRAZINE SODIUM—The monohydrated sodium salt of 2 sulfanilamidopyrazine— $C_{10}H_8N_2O_2S Na H_2O$ (M W 290.28)

Actions and Uses—Sodium sulfapyrazine may be administered intravenously when oral administration of sulfapyrazine is not feasible or when there is urgent need for the establishment of adequate blood levels of the drug. Oral administration should be started if possible, with the initial injection of the sodium salt, and intravenous administration discontinued as soon as possible. This drug should not be injected intramuscularly or intraspinally.

Dosage—Sodium sulfapyrazine is dissolved in sterile distilled water to make a 5 per cent solution which is alkaline with a pH of about 9.3. The drug is injected slowly not more than 5 cc per minute. The initial dose is 0.066 Gm per kilo of body weight.

level is 5 to 10 mg

Tests and Standards—

Sulfapyrazine sodium occurs as a white odorless bitter tasting powder, which darkens on exposure to light. It is freely soluble in water (1 Gm. in 3.33 cc at 25 C), very soluble in acetone, slightly soluble in alcohol and insoluble in ether and chloroform. Aqueous solutions of sulfapyrazine sodium may absorb carbon dioxide to cause precipitation of sulfapyrazine. The pH of a 10 per cent aqueous solution is 9.1.

at 100 C. The dry residue must be less than 1.0 per cent under Sulfapyrazine N. N. R.

Dissolve 0.5 Gm. of sulfapyrazine sodium in 25 cc of distilled water the solution is clear not more than a pale yellow, and meets the requirements for heavy metals given under Sulfapyrazine N. N. R.

Dry an accurately weighed portion of sulfapyrazine sodium at 110 C. for four hours the loss in weight is not less than 6.1 per cent nor more than 6.4 per cent. Incinerate 0.2 Gm. of anhydrous sulfapyrazine sodium accurately weighed with the addition of 0.3 cc of sulfuric acid.

Ignite until the carbon residue has been burned off, add 0.5 cc of sulfuric acid, heat gently to drive off the excess acid, and ignite to constant weight. The weight of sodium sulfate formed is not less than 24.8 per cent nor more than 26.2 per cent.

Dissolve about 0.5 Gm of each substance in 10 cc of water, weigh, in 10 cc contained in a 250 cc flask, with tenth molar sodium nitrite solution. An immediate blue streak obtained when a glass rod dipped into the solution is drawn across a smear of starch-iodide paste on white filter paper (or clear glass plate). The solution should retain this endpoint for thirty seconds. Each cubic centimeter of tenth molar sodium nitrite corresponds to 0.02723 Gm of anhydrous sulfapyridine sodium. The amount of sulfapyridine sodium found corresponds to not less than 99.0 per cent nor more than 101.0 per cent.

MEAD JOHNSON & COMPANY

Sodium Sulfapyridine; 5 Gm bottles

SULFAPYRIDINE SODIUM.—The monohydrate sodium salt of 2 sulfanilamidopyridine

Actions and Uses.—The monohydrate sodium salt of sulfapyridine has the same therapeutic activities and properties as sulfapyridine. At the present time it has been proved effective in severe pneumococcic, meningococcic, hemolytic streptococcus and severe gonococcic infections.

Dosage.—The usual initial dose of the drug for patients severely ill with pneumonia is based on 0.06 Gm per kilogram of body weight. The drug is weighed out and is then dissolved in sufficient sterile distilled water to make a 5 per cent solution. This solution will have a pH of about 10.8. It should not be sterilized by boiling, is unstable under such conditions, and should not be dissolved in sodium chloride, dextrose solutions, or used parenterally only intravenously and at the rate of 5 cc per minute. Solutions

sulfapyridine sodium is considered necessary, it is administered in such doses at intervals of about eight hours. When the sodium salt of sulfapyridine is being used, frequent determinations of the concentration of sulfapyridine in the blood should be made.

Tests and Standards—

Sulfapyridine sodium is a white, odorless, practically tasteless crystalline powder. It is soluble to the extent of 75 Gm in 100 cc of water at 25°C, soluble in alcohol, very sparingly soluble in hot acetone. The aqueous solution is alkaline to phenolphthalein, its pH is approximately 11.5. Precipitate an aqueous solution of sulfapyridine

sodium with diluted acetic acid filter and wash with ice cold water, dry at 100 C the precipitate melts between 190 and 192 C The substance imparts a yellow color to the nonluminous flame The amount of free chloride and/or sulfate ions does not exceed 0.01 per cent chloride ion or 0.02 per cent sulfate ion (U S P XII p 676) The test for heavy metals (U S P XII p 586) is negative Boil 0.5 Gm in 5 cc of water with 5 cc four normal sodium hydroxide solution no odor of ammonia is noticeable

Transfer to a weighing bottle about 0.1 Gm of sulfapyridine sodium accurately weighed and dry in the oven at 105 C overnight or 18 hours the loss in weight is not less than 6.0 per cent nor more than 6.5 per cent

Transfer the equivalent of about 5 to 25 mg of sulfapyridine sodium accurately weighed to a micro Kjeldahl digestion flask of about 50 cc capacity, add 2 to 10 cc of concentrated sulfuric acid 10 to 50 mg of selenium 50 to 100 mg of potassium sulfate and 10 to 50 mg of copper sulfate depending on the amount taken and place on an electrically heated digestion rack with a glass hood attached Heat the

FRI LILLY & Co

Sodium Sulfapyridine Monohydrate Ampuls 2 Gm
4 Gm and 6 Gm

MERCK & Co, Inc

Sulfapyridine Sodium Monohydrate (Powder) bulk

SULFATHIAZOLE SODIUM

thiazole —

thiazole.

than 99 per cent of $C_{10}H_{10}N_4O_2S_2Na$ — 0.5

Anhydrous sulfathiazole sodium has the following empirical formula $C_6H_4O_2N_4S_2Na$ (M W 277.3)

For description and standards see First Bound Supplement U S Pharmacopeia XII under Sulfathiazole Sodium

Actions and Uses—The sodium salts of sulfathiazole have the same therapeutic activities as sulfathiazole This compound has proved to be of value in the treatment of severe pneumococcal, meningococcal staphylococcal and gonococcal infections

Dosage—The usual initial dose of the drug for patients severely ill with pneumonia is based on 0.06 Gm per kilogram of body weight Solutions of the drug should be prepared in

the same manner as has been advised for solutions of sulfapyridine sodium, and the same precautions should be followed in respect to its administration

ABBOTT LABORATORIES

Sterile Sodium Sulfathiazole Anhydrous 5 Gm ampuls

LEDGER LABORATORIES, INC

Solution Sodium Sulfathiazole 25% W/V 10 cc ampuls

MERCK & Co., INC

Sulfathiazole Sodium Sesquihydrate (*Powder*) 30 Gm
113 Gm and 453 Gm

E R Squibb & Sons

Sulfathiazole Sodium Anhydrous, Sterilized 5 Gm.
vials

Sulfathiazole Sodium Sesquihydrate (Not Sterilized)
50 Gm bottles

Sulfathiazole Sodium Sesquihydrate (*Powder*) 5 Gm
bottle

WINTHROP CHEMICAL COMPANY, INC

Sulfathiazole Sodium Anhydrous (*Powder*) 1 Gm
ampuls and 5 Gm bottle

S
5

ODIUM—Sterile
d at 100° C. for
 $C_8H_8N_2O_2S_2Na$

—U S P

For description and standards see First Bound Supplement
U S Pharmacopeia XII under Sterile Sulfathiazole Sodium

Actions Uses and Dosage—Same as for Sulfathiazole Sodium

Antibiotics

PENICILLIN—A solid extract of organic nature obtained from certain molds which possesses the property of being able to inhibit the growth of and even occasionally actually to destroy certain bacteria. It may be prepared as several salts including sodium calcium and ammonium salts

Actions and Uses—Penicillin belongs to a class of agents frequently referred to as antibiotics and antimicrobial agents of biologic origin. At present penicillin is prepared by culture methods and not synthetically. In finished form the powder

usually has a brown or yellow appearance and is marketed in air tight ampuls. The material is unstable in air, hygroscopic and subject to rapid reduction in potency on exposure to heat and acids. Thus the ampuls are stored in the refrigerator and the contents put into solution only as needed. Penicillin is very soluble in water and in saline and dextrose solutions. At present the potency of penicillin preparations is determined by biologic assays, a method which essentially is concerned with the inhibition of the growth of a certain strain of *Staphylococcus aureus* in special medium, this is compared with a standard, and the result is expressed in Oxford units. All specimens also are examined for moisture content, freedom from pyrogens, sterility and toxicity.

Penicillin is indicated in staphylococcal infections with and without bacteremia, clostridial infections, hemolytic and anaerobic streptococcal infections, pneumococcal, gonococcal and meningococcal infections, and the complications caused by such infections. It may prove valuable in syphilis, actinomycosis and bacterial endocarditis, but such use is yet in the experimental stage. Subsequent uses depend on current and forthcoming research.

Dosage—Penicillin may be administered intravenously, intramuscularly, intracisternally and topically. Subcutaneous injections may be painful. Treatment may consist of repeated intramuscular or constant intravenous injections. The contents of an ampul, or ampuls, are dissolved in sterile, pyrogen free distilled water or isotonic solution of sodium chloride. For intravenous injection, concentrations of 1,000 to 5,000 units per cubic centimeter are prepared for direct injection, or 25 to 50 units per cubic centimeter for constant intravenous therapy.

severity of infection, but the objective is to bring the infection under control as quickly as possible. Inadequate dosage may create penicillin resistance in the invading organisms. Penicillin is excreted rapidly, and injections should be repeated every three or four hours unless continuous infusion is employed. In serious infections with or without bacteremia an initial dose of 15,000 to 20,000 units followed by constant infusion to supply 2,000 to 5,000 units every hour or, in the absence of constant injection, 10,000 to 20,000 units injected intramuscularly every three or four hours may be employed. After the temperature has returned to normal, the penicillin may be stopped, but the course of the disease must be watched carefully.

In chronically infected injuries, the dosage may be 5 000 to 10,000 units or more if indicated every two to four hours with local treatment as indicated. In no instance should proper surgical intervention be omitted. For sulfonamide resistant gonorrhea, 10 000 units every three hours intramuscularly or intravenously for ten doses may be administered. Treatment depends on findings of culture of exudate.

ABBOTT LABORATORIES

Penicillin (Sodium Salt) • Vials containing 100 000 Oxford units

BRISTOL LABORATORIES, INC

Penicillin Sodium Salt 20 cc vials containing 100 000 Oxford units

BURROUGHS WELLCOME & Co, INC

Penicillin Sodium 100 000 Oxford unit bottles

CONSUMMUM SOLVENTS CORPORATION

Penicillin Sodium Salt 100 000 Oxford unit vials

Penicillin Calcium Salt 100 000 Oxford unit vials

HYDIN CHEMICAL CORPORATION

Penicillin Calcium Salt 100 000 Oxford unit and 200 000 Oxford unit ampuls and vials

Penicillin Sodium 100 000 Oxford units

LAKESIDE LABORATORIES, INC

Penicillin Sodium 100 000 Oxford units in 20 cc vials and 100 000 Oxford units in 20 cc vials packaged with an accompanying 20 cc vial of isotonic solution of sodium chloride

LEDERLE LABORATORIES, INC

Penicillin (Sodium Salt) Vials containing 100 000 Oxford units

THE LILLY & Co

Penicillin (Calcium Salt) 100 000 and 200 000 Oxford unit ampuls

Penicillin (Sodium Salt) Ampuls of 100 000 and 200 000 Oxford units

McNEIL LABORATORIES, INC

Penicillin Sodium 100 000 Oxford units in 20 cc vials

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WARREN TEED PRODUCTS COMPANY

Penicillin Sodium Salt 100 000 Oxford unit vials

WINTHROP CHEMICAL COMPANY, INC

Penicillin Sodium Ampuls Each ampul contains 100 000 Oxford units

WYETH INCORPORATED

Penicillin Sodium Vials of 100 000 Oxford units

Penicillin Calcium Vials of 100 000 Oxford units

TYROTHRICIN—(See under Local Anti Infection)

Antiprotozoan Agents

Antimony Compounds

ANTIMONY THIOGLYCOLLAMIDE—The triamide of antimony thioglycollic acid $Sb(SCH_2CO NH_2)_3$. It contains not less than 30 per cent of antimony

Actions and Uses—Antimony thioglycollamide and antimony sodium thioglycollate are used in the treatment of granuloma venereum and are proposed for use in the treatment of lympho granuloma venereum and kala azar. These substances have been found to be less toxic and less irritating than antimony and potassium tartrate. The thioglycollamide has proved to be somewhat more toxic than the thioglycollate. The former is also less soluble but it has the advantage of being more stable. The drugs are used intramuscularly or intravenously.

Dosage—The usual intramuscular or intravenous dose employed by Randall is 0.08 Gm dissolved in 20 cc of sterile water every second day until from 15 to 25 injections have been given. He recommends that at least 12 injections be given after the first healing has taken place to insure permanent cure. Its solutions are incompatible with solutions of the fixed alkalis.

Tests and Standards—

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Dissolve 0.2 Gm. of antimony thloglycollamide in 5 cc. of hydrochloric acid, add 10 cc. of freshly prepared stannous chloride solution and allow to stand 10 minutes. No brownish tint or precipitate is visible if viewed from above over a white surface (*arsenic*). A blank test should be carried out, using the same quantities of reagents.

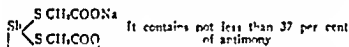
Weigh accurately from 0.2 to 0.3 Gm. of antimony thloglycollamide, dissolve it in about 100 cc. of warm water, add 1 cc. of diluted hydrochloric acid, pass in hydrogen sulfide until precipitation is complete and allow to stand 10 minutes. Collect the antimony sulfide in a weighed Gooch crucible, wash it successively with water containing hydrogen sulfide, alcohol ether, carbon disulfide, alcohol and ether, dry the residue at 100 C. and weigh. The antimony sulfide obtained corresponds to not less than 10 per cent of antimony.

HYNSON, WESTCOTT & DUNNING, INC.

Antimony Thloglycollamide (Powder): bulk

Solution Antimony Thloglycollamide, 0.4 per Cent.
10 cc. and 20 cc. ampuls

ANTIMONY SODIUM THIOGLYCOLLATE—The compound formed by dissolving antimony trioxide in a solution of a mixture of sodium thloglycollate and thloglycollic acid



Actions and Uses—The same as for antimony thloglycollamide. It is more soluble than antimony thloglycollamide, and in higher dosages it appears to be less toxic.

Dosage—From 0.05 to 0.1 Gm. dissolved in 10 to 20 cc. of sterile water every third or fourth day until from 15 to 25 infectives have been given. Its solutions are incompatible with solutions of the fixed alkalis.

Tests and Standards

Antimony and sodium thloglycollate is a white or light pinkish powder which on heating first loses off its odor, then on further heating is volatile in a steam.

Add a drop of diluted hydrochloric acid to 2 cc. of a dilute solution of antimony and sodium thloglycollate (1 in 10) and add two drops of 1 per cent ferric chloride solution. A brown precipitate is formed. Add a drop of 1 per cent sodium acetate to the mixture and shake. The precipitate redissolves. Add a few drops of sodium hydroxide solution and the mixture of antimony and sodium thloglycollate will be precipitated. Filter the precipitate, wash with water, add a few drops of diluted hydrochloric acid and pour in hydrogen sulfide. An orange-colored precipitate is formed.

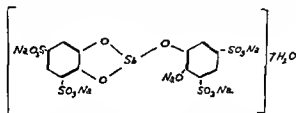
Weigh accurately from 0.2 to 0.3 Gm. of antimony and sodium thloglycollate, dissolve it in about 100 cc. of warm water, add 1 cc. of diluted hydrochloric acid, pass in hydrogen sulfide until precipitation is complete and allow to stand 10 minutes. Collect the antimony sulfide in a weighed Gooch crucible, wash it successively with water containing hydrogen sulfide, alcohol ether, carbon disulfide, alcohol and ether, dry the residue at 100 C. and weigh. The antimony sulfide obtained corresponds to not less than 37 per cent of antimony.

HYNSON, WESTCOTT & DUNNING, INC

Antimony Sodium Thioglycollate (Powder): bulk

Solution Antimony Sodium Thioglycollate 0.5 per Cent
10 cc and 20 cc ampuls

FUADIN—Stibophen—Sodium antimony 111 bis catechol 2,4 disulfonate — $[(\text{NaO}_2\text{S})_2\text{C}_6\text{H}_2(\text{O})_2)_2\text{Sb}(\text{OC}_6\text{H}_3\text{ONa}(\text{SO}_3\text{Na}))_2] \cdot 7\text{H}_2\text{O}$ It contains 13.6 per cent of trivalent antimony



Actions and Uses—Fuadin is proposed for use in the treatment of granuloma venereum and of schistosomiasis (bilharziasis). Its action is reported to be more rapid and efficient in early granuloma venereum than in the later stages when there is scar formation. It is necessary to keep the treatment up for some time after all evidence of the disease has disappeared. In schistosomiasis it is indicated together with iron as the treatment of choice in the intestinal stage of the disease. The iron salts should be given after the completion of the treatment and not concurrently. The anemia, when present, is apparently due to a prolonged iron deficiency.

Dosage—Intramuscularly (rarely intravenously), first day 1.5 cc, second day 3.5 cc, and on the third, fifth, seventh, ninth, eleventh, thirteenth and fifteenth days 5 cc, a total of 40 cc of the 6.3 per cent solution. Following healing in a week or two weeks the course may be repeated and thereafter the drug is given once a week and then every fourteen days for several weeks to prevent relapse.

Tests and Standards—

Fuadin is supplied only in an approximately 6.3 per cent solution with not more than 0.125 per cent sodium bisulfite as a preservative. The solution is clear, odorless and nearly colorless; it possesses a slightly saline taste and acquires a faint pink color on standing in the light. The specific gravity of fuadin solution is not less than 1.037 nor more than 1.041 at 25°C.

To 2 cc of solution add 0.5 cc of diluted hydrochloric acid. 10 cc
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To 1 cc of fuadin solution, add 2 cc of a solution of magnesium uranyl acetate a yellow crystalline precipitate appears. To 1 cc of the solution add 2 drops of diluted nitric acid and 2 drops of silver nitrate solution; not more than faint opalescence is produced immediately (*chloride*).

To 2 cc of fuadin solution add 20 cc of bromine water and 1 cc of diluted hydrochloric acid, expel the bromine by boiling and add 1 cc of ammonium thiocyanate solution no red color appears (*iron*). To 2 cc. of fuadin solution add 1 cc of ammonium hydroxide and 2 drops of ammonium oxalate solution no precipitate appears (*calcium*).

To 2 cc. of fuadin solution in a glass stoppered flask, add 2 cc of diluted acetic acid and 0.6 cc of formaldehyde solution and allow to stand five minutes. Add an excess of fiftieth normal iodine solution and, after five minutes, titrate the excess with fiftieth normal sodium thiosulfate, using a 1 per cent starch solution as indicator the trivalent antimony content is not less than 0.81 nor more than 0.88 Gm per hundred cubic centimeters.

Transfer 5 cc of fuadin solution to a 250 cc beaker and add 18 cc of diluted hydrochloric acid and 32 cc of water. Evaporate the solution to about 5 cc and neutralize with sodium hydroxide solution. Transfer to a nickel crucible, evaporate to dryness and add 5 Gm of sodium hydroxide containing 5 per cent potassium nitrate. Fuse the mixture and heat until it is free from organic matter and dissolve the cooled melt in 100 cc of water. Acidify the solution with diluted hydrochloric acid, add 1 Gm of tartaric acid, filter, and precipitate the sulfates by adding 5 cc of a 10 per cent barium chloride solution. Digest on a steam bath for at least three hours, filter on a Gooch crucible, ignite and weigh the sulfur content is not less than 0.847 and not more than 0.950 Gm per hundred cubic centimeters.

WINTHROP CHEMICAL COMPANY, INC.

Solution Fuadin: 35 cc. and 5 cc ampuls. Each 1 cc contains fuadin, 64 mg., sodium bisulfite not more than 0.125 per cent.

U S patents 1549,154 (Aug 11, 1925, expired) and 1873,668 (Aug 23, 1932, expires 1949) U S Trademark 304950

Arsenic Compounds

In some of the compounds listed in this chapter, the arsenic is pentavalent; in others it is trivalent. A typical arsenic reaction results only from the trivalent arsenic, and in order to secure this action from those compounds containing pentavalent arsenic, their arsenic must be reduced to the trivalent form, this is done by the body, but the rate at which the reduction occurs varies greatly with the different compounds. In some cases, the desirable, as well as the undesirable, effects produced by these compounds are due to the arsenic which is slowly rendered active, in others the therapeutic effects may be due, at least in part, to the unaltered molecules. The diseases in which arsenic therapy has proved useful are particularly those caused by protozoa. Inorganic arsenic will kill protozoa, but it cannot be administered so as to reach the protozoa in fatal quantity. In the body, the organic compounds are less toxic to mammals and more toxic to protozoan parasites. In this way they become available for combating trypanosomiasis, treponematoses, spirillosis and other protozoan infections.

Among the advantages claimed for, or known to be possessed by, these compounds, the following may be mentioned. In those known to produce their effects through the liberation of arsenic, the arsenic is liberated slowly, some remain in the circulating blood for a much longer period than do inorganic arsenic compounds and thus remain longer in contact with parasites which it is desired to kill, some are specifically etiotropic, that is, they have a much greater affinity for the parasites causing the disease than they have for the tissues of the host.

Arsphenamine and analogous preparations of arsenic used intravenously come under the federal law covering serums, viruses, toxins and analogous products, and are subject to the same control.

COMPOUNDS CONTAINING TRIVALENT ARSENIC

According to Ehrlich's view, only trivalent arsenic is markedly toxic to spirochetes, trypanosomes, etc., hence he introduced a number of such compounds. Of these only the compounds in which the toxicity is reduced or modified by the introduction into the molecules of certain groups are listed below. These compounds have, according to Ehrlich, a special affinity for certain organisms particularly spirochetes while their toxicity for the higher animals is comparatively low. The exact fields of usefulness of these compounds and their limitations, and also the best methods of administering them, are still under discussion.

The toxic actions of arsphenamine are ascribed to the arsenic component in some cases. In other cases the decomposition of the solution has been assigned as a cause. Undoubtedly some reactions are due to idiosyncrasies on the part of the patient. However, there is seen a large group of these cases which must be explained otherwise. Certainly, improper technique in the preparation of the drug as well as the improper (for example, too rapid) administration of the arsphenamines may add to the inherent toxicity. The administrator should always carefully observe the directions supplied by the manufacturers. If this be done and there are still reactions, then one should look elsewhere for the causation.

The water used should be if possible freshly distilled and freshly sterilized. All chemicals should be pure. Any rubber tubing employed for the first time should be soaked over night in 5 per cent sodium hydroxide solution then boiled in distilled water and thoroughly washed with the same. Some reactions are undoubtedly due to administration of the drug to a patient on a full stomach or to one not properly prepared by previous catharsis. It is always well to start the use of arsenicals with a small dose—because of possible idiosyncrasies.

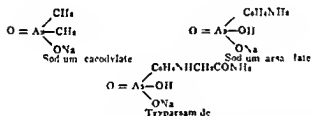
One should not be too much alarmed in a fresh case of syphilis by the reaction seen after the first injection of the arsphenamines—the Herxheimer reaction. It is that phenom-

non of the reaction of the disease to the arsphenamine in which there is a rise of temperature headache possible nausea malaise and marked accentuation of the cutaneous and mucous membrane symptoms. One should be concerned however, if with succeeding injections there are promptly recurring reactions in the form of gastritis itching of the skin urticaria conjunctivitis fixed areas of dermatitis that flare up with each new injection and more or less generalized dermatitis or jaundice. In addition there are sometimes noted generalized exfoliative dermatitis purpura hemorrhagica aplastic anemias acute yellow atrophy and encephalitis.

The best treatment of these conditions is prophylaxis, and these drugs should never be readministered without inquiry of the patient and examination of the skin as to possible pruritus jaundice cutaneous eruptions or other symptoms. Moreover a urine examination should always be a preliminary.

Arsphenamines are contraindicated or should be used with special caution in diseases of the eye of a nonsyphilitic character, in severe affections of the heart and blood vessels the

COMPOUNDS CONTAINING PENTAVALENT ARSENIC



In one of the compounds listed above the arsenic is in combination with an alkyl group and is thus analogous to the cacodylates. In the others the arsenic is in combination with aniline and is thus analogous to arsenic acid.

Arsanilic acid is derived from arsenic acid $\text{AsO}(\text{OH})_2$ by replacing one hydroxyl by aniline (phenylamine) $\text{C}_6\text{H}_5\text{NH}_2$. Related compounds are made by substituting derivatives of aniline.

The compounds containing pentavalent arsenic are comparatively nontoxic when introduced into the animal system until changes take place that liberate the arsenic. When they are slowly decomposed they produce favorable effects. If the reduction takes place with greater rapidity they may produce ordinary arsenic poisoning.

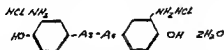
Sodium cacodylate is excreted partly unchanged and partly as cacodylic oxide, which gives a foul odor to the breath, perspiration etc. Further changes yield products containing inorganic, trivalent arsenic, by which the therapeutic effects if there are any, are produced. It is not used in the treatment of syphilis.

Sodium arsaniolate acts with especial violence on the optic nerve, producing optic atrophy, frequently resulting in permanent blindness. This may occur unfortunately even with therapeutic doses. It is not used in the treatment of syphilis.

Tryparsamide is a powerful trypanocide and only slightly treponemacidal. The drug, according to studies of Voegtlin and co workers, when injected intravenously results in pronounced penetration of the nervous system tissue. This may explain its value in the treatment of resistant syphilis of the central nervous system. It may be used following malaria therapy. The suggestion has been made by Young and Loevenhart that the effect on the optic nerve frequently seen after triparasamide is due to the presence of the amino group in the para position to the arsenic (Stokes). Because of this fact the physician should exercise great caution in the use of this drug.

Compounds Containing Trivalent Arsenic

ARSPHENAMINE — Diaminodihydroxyarsenobenzene Dihydrochloride — Contains not less than 30 per cent and not more than 32 per cent of arsenic (As) and complies with the requirements of the national Institute of Health United States Public Health Service U S P



For description and standards see the U S Pharmacopoeia under Arspenamine.

Actions and Uses.—Arspenamine is useful as a specific remedy for syphilis in all stages. According to available data in incipient tabes, early paresis, epilepsy and cerebrospinal syphilis the drug can be employed with the prospect of most benefit in those cases in which its use is begun early.

The drug is used in the spirillum affections such as relapsing fever and frambesia.

The remedy is contraindicated in severe disturbances of the circulatory organs, advanced degenerations of the central nervous system and cachexias unless these are a direct result of syphilis. It is also contraindicated in patients who have pronounced idiosyncrasy against arsenic.

It has been employed successfully in various types of syphilitic diseases of the eyes. As a rule in such cases it is well to give a preliminary course of mercury or bismuth injections in order to obviate the danger of a Herxheimer reaction. Repeated injections should be given. It may be used up to 0.01 Gm per kilogram of body weight but it is better to keep under this dose.

Dosage—Usually from 0.2 to 0.4 Gm though 0.6 Gm may be given the smaller doses are more extensively used.

For children from 0.1 to 0.2 Gm. In infants doses of from 0.02 to 0.1 Gm may be used. The dose should be varied according to the strength and condition of the patient. The intravenous method is preferable and is to be recommended.

For intravenous injection one should proceed thus:

The ampul containing the drug is immersed in alcohol in order to be a hot water bath.

tion using 0.85 cc to every 0.1 Gm of the drug. Thus 0.6 Gm of the drug would require 5.1 cc of normal alkali. A precipitate of the base is first formed which after the contents are carefully agitated is again brought into solution the fluid being strongly alkaline. Filter through a fine filter.

gauze 4 ply and dilute to

to make 25 cc for each 1 Gm of drug. Allow to stand for 30 minutes before using. At least one minute should be allowed for each 25 cc of the solution to flow into the vein using the gravity method. The directions accompanying the drug as to temperature of the water etc should be followed. The contents of a tube should be mixed at once after opening and under no circumstances should the contents of a tube damaged in transportation or any remnants of the powder from previously opened tubes be used. In all cases the skin should be disinfected with tincture of iodine or with alcohol.

ABBOTT LABORATORIES

Arsphenamine 0.4 Gm 0.6 Gm 1.0 Gm and 3.0 Gm ampuls

DIARSENOL COMPANY INC

Diarsenol 0.1 Gm 0.2 Gm 0.3 Gm 0.4 Gm 0.5 Gm 0.6 Gm 1.0 Gm 2.0 Gm and 3.0 Gm ampuls

MERCK & CO INC

Arsphenamine 0.1 Gm 0.2 Gm 0.3 Gm 0.4 Gm 0.5 Gm 0.6 Gm 1.0 Gm and 3.0 Gm ampuls

WINTHROP CHEMICAL COMPANY, INC.

Salvarsan (Powder): bulk Arsphenamine

Salvarsan: 0.1 Gm, 0.2 Gm, 0.3 Gm, 0.4 Gm, 0.5 Gm, 0.6 Gm, 1.0 Gm, 1.2 Gm, 2.0 Gm and 3.0 Gm ampuls

Description—

Bismuth
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salts It contains approximately 13 per cent of arsenic and 24 per cent of bismuth

Actions and Uses—For the treatment of syphilis. The drug is said to be somewhat slower in its action than intramuscularly administered sulfarsphenamine or intravenously administered neoarsphenamine. Some pain at the site of injection may be noted.

Dosage—Bismarsen is administered intramuscularly. The initial dose is 0.1 Gm, succeeding doses are 0.2 Gm. A 0.1 Gm dose is dissolved, at the same time of administration, in 1 to 2 cc of a sterile aqueous solution of 0.25% butyn sulfate. Weekly doses may be later increased to biweekly doses in courses of treatment of twenty doses, or more.

Tests and Standards—

Bismarsen is prepared by adding a solution of potassium bismuth tartrate in water to an aqueous solution of 3,3'-diamino-4,4'-dihydroxy-arsenobenzene N,N'-dimethylene sulfonate, dissolving the precipitate with a measured quantity of sodium hydroxide solution, precipitating by pouring the clear solution into a methyl alcohol-ether mixture and filtering off the precipitate and drying it in vacuo.

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marsen

in a test tube and at the mouth of the tube hold a strip of filter paper moistened with 5 per cent cadmium chloride solution the paper turns yellow in four minutes

Transfer about 0.4 Gm of bismarsen accurately weighed, to a

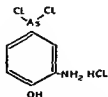
ABBOTT LABORATORIES

Bismarsen 0.1 Gm and 0.2 Gm ampuls, accompanied respectively, by 1 cc and 1½ cc ampuls of a sterile, aqueous solution of 0.25% butyn sulfate

U S patent 1,605,691 (Nov 2 1926 ext red) U S trademark 230,625

DICHLOROPHENARSINE HYDROCHLORIDE

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Dichlorophenarsine Hydrochloride is usually distributed as a mixture with buffering agents and suitable substances to

render its solution physiologically compatible with human blood. The label must indicate the names of the admixed substances and the composition of the mixtures (containing Dichlorophenarsine Hydrochloride as the only active therapeutic agent) shall be approved by the National Institute of Health. Mixtures contain total arsenic equivalent to not less than 92.5 per cent and not more than 107.5 per cent of the labeled amount of Dichlorophenarsine Hydrochloride. Mixtures also meet the requirements for identification loss on drying, thermostability, completeness of solubility and storage.

"Dichlorophenarsine Hydrochloride and its mixtures must be prepared in an establishment licensed for the purpose by the United States government upon the recommendation of the Surgeon General of the United States Public Health Service. Each lot of the product before being offered for sale must comply with the toxicity, labeling and other requirements of the National Institute of Health and be released by the Institute—U S P

For description and standards see the U S Pharmacopeia under Dichlorophenarsine Hydrochloride

Actions and Uses—In recent literature may be found reports of an arsenical antisyphilitic agent which apparently was discovered in the early part of this century but was cast aside as being too toxic for clinical use. Some years later there were published reports on its use in animals and in the treatment of yaws and human syphilis. It was not until 1941 that 3-amino-4-hydroxyphenyl arsenic trioxide was synthesized by the factory for the studies were based on which would provide a very low pH .

The preparations now available on the market contain sufficient alkaline buffering agent to make neutral a prepared solution for injection. They contain approximately 26 per cent of trivalent arsenic. On the addition of sterile distilled water to an ampul containing the mixture of dry dichlorophenarsine hydrochloride and alkaline buffer a reaction takes place with the result that arsenoxide is supposed to be formed. It has been claimed that the latter agent is the therapeutically active part of the compound.

(A preliminary report of the Council appeared in *THE JOURNAL* Sept 25 1943 p 208)

Dosage—Initial dose for adults 45 mg intravenously. The second dose may be increased to 67 or 68 mg. The maximum dose may be regarded as 68 mg. Injections may be given every four to five days since the drug is excreted rapidly.

For children the initial dose should not exceed 0.5 mg per kilogram of body weight. The later doses should average between 0.5 mg and 1.0 mg per kilogram of body weight.

ABBOTT LABORATORIES

Dichlorophenarsine Hydrochloride Ampuls 45 mg 68 mg and multiple dose ampuls of 0.45 Gm and 0.68 Gm

L. R. SQUIBB & SONS

Clorarsen 45 mg and 67 mg ampuls Each ampul contains the stated quantity of dichlorophenarsine hydrochloride admixed with three and one third times its weight of a mixture containing sodium citrate 96 parts and sodium carbonate 4 parts

Clorarsen 0.45 Gm and 0.67 Gm ampuls Multiple dose containers Each ampul contains the stated quantity of dichlorophenarsine hydrochloride admixed with three and one third times its weight of a mixture containing sodium citrate 96 parts and sodium carbonate 4 parts

WINTHROP CHEMICAL CO. INC.

Dichlorophenarsine Hydrochloride Ampuls 45 mg and multiple dose ampuls 0.45 Gm Each ampul contains in addition to each 45 mg of dichlorophenarsine hydrochloride 25 mg of anhydrous sodium carbonate 45 mg of sodium chloride and 80 mg of sucrose

0.102 Gm of sucrose

OXOPHENARSINE HYDROCHLORIDE—Napharsen — 3 amino 4 hydroxyphenyl arsineoxide hydrochloride — $C_6H_4AsO_2N \cdot HCl$ — M. W. 235.49



is dried in a vacuum desiccator for 4 hours contains not less than 95 per cent of total arsenic

of the product before being offered for sale must comply with the toxicity labeling and other requirements of the National Institute of Health and be released by the Institute —U. S. P.

For description and standards see U. S. P. XII First Bound Supplement under Oxophenarsine Hydrochloride

Actions and Uses—Oxophenarsine hydrochloride is proposed for the treatment of syphilis. It is stated to exhibit a relatively constant parasitocidal value. It is claimed to have a rapidly beneficial effect particularly on early syphilis with disappearance of spirochetes, healing of lesions and reversal of positive Wassermann reactions in a large percentage of cases. The reactions following the use of oxophenarsine hydrochloride are less severe than those observed after the use of the arsphenamines.

Dosage—Intravenously 0.03 Gm for women and 0.04 Gm for men initially. The dose may be increased at the second injection to 0.04 Gm for women and 0.06 Gm for men. The maximum dose which should not be given any patient at the first injection may be regarded as 0.06 Gm. Injection may be given every four or five days since it is excreted very rapidly from the kidney. For children the initial dose should not exceed 0.0005 Gm (0.5 mg) per kilogram of body weight; the total dose should average between 0.0005 and 0.001 Gm (between 0.5 and 1 mg) per kilogram of body weight.

It should be noted that the dosage of oxophenarsine hydrochloride is much lower than that of the arsphenamines.

Oxophenarsine hydrochloride is usually distributed as a mixture with buffering agents and suitable substances to render its solution physiologically compatible with human blood. The label must indicate the names of the admixed substances and the composition of the mixtures (containing oxophenarsine hydrochloride as the only active therapeutic agent) shall be approved by the National Institute of Health. Mixtures contain total arsenic equivalent to not less than 92.5 per cent and not more than 107.5 per cent of the labeled amount of oxophenarsine hydrochloride. The mixtures also meet the requirements for identification, thermostability, completeness of solubility and storage.—U S P

PANKE, DAVIS & COMPANY

Mapharsen 40 mg and 60 mg ampuls

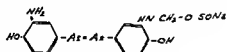
Mapharsen 0.6 Gm (multiple dose) ampuls *Caution: These ampuls are hospital packages and represent either 10 doses at 6 mg or 15 doses at 40 mg*

Each of the ampuls of mapharsen contains the stated amount of the arsenical oxophenarsine hydrochloride admixed with anhydrous sodium carbonate 4.3 per cent and anhydrous sucrose 81.4 per cent.

U S patents 2,092,028 and 2,092,036 (Sept. 7, 1937 exp. res. 1954)
U S trademark 299,173

NEOARSPHENAMINE—Consists chiefly of sodium 3,3-diamino-4,4-dihydroxyarsenobenzene N-methanal sulfoxylate. It contains not less than 19 per cent of arsenic (As) and complies

with the requirements of the National Institute of Health United States Public Health Service" U S P



For description and standards see the U S Pharmacopeia under Neoarsphenamine

Actions and Uses.—Neoarsphenamine is a modified soluble compound of arsphenamine, its action and uses are those of arsphenamine

Dosage.—Neoarsphenamine is probably less toxic than arsphenamine and since it contains less arsenic, it is given in larger doses than arsphenamine. The average dose for a man is 0.45 to 0.60 Gm, with 0.45 Gm as the minimum and possibly 0.75 Gm as the maximum only for very large men. For women, 0.45 Gm is the average if the patient is about the normal in weight, 0.3 Gm would be the minimum and 0.6 Gm the maximum, the latter dose being given only to large women. Children may be given 0.1 to 0.2 Gm. The limit dose is 15 mg per kilogram of body weight. Here again a smaller dose is preferable.

Neoarsphenamine may be administered by intravenous or subcutaneous routes. The drug is supplied as a sodium salt, freshly distilled neoarsphenamine, and should be dissolved in freshly distilled water. For this purpose as much as 0.1 Gm may be dissolved in 0.5 cc of sterile freshly distilled water, the injection is made with a syringe instead of by gravity. It is well to draw out an equal amount of blood into the syringe containing the neoarsphenamine solution before reinjecting into the blood stream. It should be injected very slowly.

The ampule containing the drug is immersed in alcohol to detect a possible crack, then carefully wiped off, the neck filed and the ampule used. For this purpose as much as 0.1 Gm may be dissolved in 0.5 cc of sterile freshly distilled water, the injection is made with a syringe instead of by gravity. It is well to draw out an equal amount of blood into the syringe containing the neoarsphenamine solution before reinjecting into the blood stream. It should be injected very slowly.

The ampule containing the drug is immersed in alcohol to detect a possible crack, then carefully wiped off, the neck filed and the ampule used.

Neoarsphenamine may undergo deterioration in the ampule and care should be exercised to use a drug of normal color and free solubility. The drug in fresh solution should be of canary

yellow color. This drug should preferably be kept in a cool dark room or ice box and be not more than 6 months old

Caution—Solutions of Neoarsphenamine must be freshly prepared when required for use. The solution should not be shaken during its preparation. U S P

ABBOTT LABORATORIES

Neoarsphenamine. 0.15 Gm, 0.3 Gm, 0.45 Gm, 0.6 Gm, 0.75 Gm, 0.9 Gm, 1.5 Gm, 3.0 Gm and 4.5 Gm ampuls

Neoarsphenamine and Metaphen: Packages containing five ampules of neoarsphenamine, 40 mg each and one bottle of metaphen solution 1:1,000 (20 cc)

Actions and Uses—Neoarsphenamine and metaphen is proposed for the treatment of Vincent's gingivitis and stomatitis

Dosage—Neoarsphenamine 0.04 Gm is dissolved with 4 cc of the 1:1,000 aqueous solution of metaphen and the resultant solution is applied topically

DIARSENOL COMPANY, INC

Neodiarsenol: 0.15 Gm, 0.3 Gm, 0.45 Gm, 0.6 Gm, 0.75 Gm, 0.9 Gm, 1.5 Gm, 1.8 Gm, 3.0 Gm and 4.5 Gm ampuls

MERCK & CO, INC.

Neoarsphenamine: 0.15 Gm, 0.3 Gm, 0.45 Gm, 0.6 Gm, 0.75 Gm, 0.9 Gm, 3.0 Gm and 4.5 Gm ampuls

E R SQUIBB & SONS

Neoarsphenamine: 0.15 Gm, 0.3 Gm, 0.45 Gm, 0.6 Gm, 0.75 Gm, 0.9 Gm, 3.0 Gm and 4.5 Gm ampuls

WINTHROP CHEMICAL COMPANY, INC.

Neosalvarsan (Powder) • bulk Neoarsphenamine

Neosalvarsan: 0.15 Gm, 0.3 Gm, 0.45 Gm, 0.6 Gm, 0.75 Gm, 0.9 Gm, 1.5 Gm, 1.8 Gm, 3.0 Gm and 4.5 Gm ampuls

SILVER ARSPHENAMINE — Arsphenamina Argentea. — Sodium Silver Arsphenamine. — The sodium salt of silver diamino dihydroxy arseno benzene (the exact molecular formula has not been established). Silver arsphenamine contains not less than 19 per cent of arsenic and from 12 to 14 per cent of silver

Actions and Uses—Silver arsphenamine has practically the same uses as those of arsphenamine. Its claimed advantage over other arsphenamine preparations is said to be due to the introduction of the silver (nonionizable form) as a component,

thereby improving the chemotherapeutic index, presumably because of the fact that silver and its compounds have a decided antisyphilitic influence

In the presence of organic diseases of the heart, such as aneurysm and aortitis, as well as in other parenchymatous disease conditions of the glandular structures (liver and kidney), silver arsphenamine should be used only with great caution and in small doses the patient and all functions being observed most carefully

Untoward symptoms noted after the use of arsphenamine and of neoarsphenamine have likewise been seen after the use of silver arsphenamine. Argyria may occur rarely as a sequel to the use of this preparation

Dosage—From 0.1 Gm to 0.3 Gm for adults. The treatment should begin with an injection of 0.1 Gm, gradually increasing the dosage, at intervals of not less than four days, to 0.2 Gm maximum in women and 0.3 Gm in men. The larger doses are indicated only if the preparation is well tolerated by the patient. The doses of 0.2 to 0.25 Gm may be given at regular intervals of 7 days and repeated until the desired therapeutic results have been achieved. Patients with disorders of the nervous system or the eyes suffer no from severe headaches

When
employed,

In preparing the solution for injection the ampule is first tested for cracks by immersion in alcohol for 15 minutes after opening the ampule, the contents are sprinkled on the surface of 5 cc of cool (20-22°C), sterile, distilled water, contained in a small sterile flask. The silver arsphenamine will go into solution rapidly, heating and shaking must be avoided. A quantity of cool sterile solution of sodium chloride, 0.4 per cent is then added so that the final solution will approximate 20 cc of liquid per decigram (0.1 Gm) of the drug. *The solution must be administered promptly but slowly*

Tests and Standards—

Silver arsphenamine is prepared by treating the dihydrochloride of 3-diamino-4-dihydroxy-1-arsenobenzene (arsphenamine) with silver salts converting the resulting compound to the disodium salt and precipitating by means of alcohol either or acetone. The silver is not in an ionizable form.

Silver arsphenamine is a brownish black powder, unstable in air when properly dried it is free from lumps. It is readily soluble in water yielding a dark brown solution (*distinction from arsphenamine sodium arsphenamine and neoarsphenamine*). The solution has an alkaline reaction (*distinction from arsphenamine*).

The addition of dilute sodium hydroxide solution to 3 cc of an aqueous solution of silver arsphenamine (1 in 500) produces no precipitate (*distinction from arsphenamine*). On the addition of 1 cc of sodium carbonate test solution to 1 cc of silver arsphenamine solution

(1 in 20) no precipitate is formed (distinction from arsphenamine). The addition of 1 cc. of saturated solution of sodium bicarbonate to 1 cc. of silver arsphenamine solution produces a precipitate.

arsphenamine solution (1 in 20) produces a precipitate which dissolves on further addition of cc. of silver arsphenamine solution. Stals of potassium permanganate from arsphenamine, the permanganate is reduced and ammonia is evolved which may be tested by placing a moistened piece of red litmus paper in the vapors. The precipitate dissolves on addition of concentrated mineral acids.

When employed, an immediate precipitate is formed. The careful addition drop by drop, of bromine water to 3 cc. of silver arsphenamine solution (1 in 250) produces a reddish coloration, which is discharged by an excess of the reagent; there is also formed a precipitate which dissolves on addition of a larger excess of concentrated ammonia water (distinction from arsphenamine).

test solution. no precipitate
concentrated sodium chloride
silver arsphenamine causes a
reaction.)

Place about 0.2 Gm. of silver arsphenamine, accurately weighed, in an Erlenmeyer flask, and carry out the Lehmann process (described in *Pub Health Rep.* 33:1003 [June 21] 1918) through the point of decoloration. The residue is dried in a porcelain crucible, the per cent of silver is determined by the method of content.

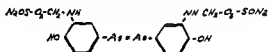
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WINTHROP CHEMICAL COMPANY, INC

Silver-Salvarsan: 0.1 Gm, 0.15 Gm, 0.2 Gm, 0.25 Gm, 0.3 Gm and 0.6 Gm ampuls

U S patent 1,127,603 (Feb 9, 1915, expired) U S trademark 161,232

SULFARSPHENAMINE — "Disodium 3,3'-diamino 4,4'-dihydroxyarsenobenzene-*N*-dimethylenesulfonate. It contains not less than 19 per cent of arsenic (As)." U S P. According to claims, it differs from neoarsphenamine in having two side chains instead of one, and in that the sulfur has a valence of four (with an extra oxygen atom) and not two as in neoarsphenamine.



For description and standards see the U S Pharmacopeia under Sulfarsphenamine.

Actions and Uses—The same as those of neoarsphenamine, it is probably somewhat more stable in solution in the presence of air, and it permits of intramuscular injection. In terms of percentages there seems to be a higher incidence of reactions following the use of sulfarsphenamine, far more in fact, than after the use of the other arsenicals employed in the treatment of syphilis. These reactions consist in (a) dermatitis, (b) hemorrhagic eruptions, (c) meningo vascular reactions, and (d) aplastic anemias. All patients under treatment with sulfarsphenamine should be followed closely by the physician for evidence of reaction. The drug has a place, and may be used by the intramuscular route in the treatment of early heredo syphilis and in certain cases where the patient has such poor veins that intravenous therapy is out of the question. Moore considers it the drug of choice, by the intramuscular route in early congenital syphilis.

Dosage—The maximum dosage by any route should probably not exceed 0.4 Gm, or at most 0.5 Gm of the dry substance.

For intramuscular or subcutaneous use the drug is dissolved in sterile, freshly distilled water in the proportion of about 0.1 Gm to 0.3 cc, the total volume being not more than 10 to 20 cc. There is probably less local reaction where a minimum of diluent is employed. For intravenous use the drug should be diluted in the proportion of 0.1 Gm to not less than 10 and preferably, 40 cc, or more, the total volume amounting to 50 to 200 cc or more. Dosage for infants is 10 mg to 15 mg per kilogram of body weight.

ABBOTT LABORATORIES

Sulfarsphenamine: 0.1 Gm, 0.2 Gm, 0.3 Gm, 0.4 Gm and 0.6 Gm ampuls

MERCK & Co., INC.

Sulfarsphenamine: 0.1 Gm, 0.2 Gm, 0.3 Gm, 0.4 Gm, 0.5 Gm and 0.6 Gm ampuls

E. R. SQUIBB & SONS

Sulfarsphenamine: 0.1 Gm, 0.2 Gm, 0.3 Gm, 0.4 Gm, 0.5 Gm, 0.6 Gm, 0.9 Gm and 3.0 Gm ampuls

WINTHROP CHEMICAL COMPANY, INC.

Sulfarsphenamine: 0.15 Gm, 0.3 Gm, 0.45 Gm, 0.6 Gm, 0.75 Gm, 0.9 Gm and 3.0 Gm ampuls

Compounds Containing Pentavalent Arsenic

ACETARSONE—Acetylaminohydroxyphenylarsonic Acid— $\text{HO-CH}_2\text{CONH-C}_6\text{H}_4\text{-As(O)}_3$ —Stovarsol—The acetyl derivative of 3-amino-4-hydroxyphenyl 1-arsonic acid—Acetarsonone contains from 27.1 to 27.4 per cent of arsenic (As)



Actions and Uses—Acetarsonone has been reported to produce favorable effects in the treatment of amebiasis. Acetarsonone is useful as a means of medication of the vagina in the treatment of *Trichomonas vaginitis*. Its use in the treatment of sarcoid has been recommended by various dermatologists. Acetarsonone has been proposed for use both in prophylaxis and in treatment in certain cases of syphilis, but the evidence is thus far inconclusive. Its use in amebic infections undoubtedly is of value though still in the experimental stage. In using acetarsonone, the physician should remember that he is working with a rather toxic arsenical preparation, which may give rise to gastrointestinal symptoms and hepatitis as well as to the same cutaneous disturbances that are found with the arsphenamines for example, urticaria, erythema of various types and even hemorrhagic eruptions. At the least sign of intolerance the physician should discontinue the use of the drug for the time being.

Acetarzone in common with other arsenicals, should ordinarily not be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow, suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa, positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

Dosage—Orally, 0.25 Gm. for adults, two or three doses a day for a period of seven days have been reported to give satisfactory results. For *Trichomonas vaginitis*, use locally in the vagina a powder containing 12½ per cent acetarzone in a mixture of equal parts of kaolin and sodium bicarbonate. Single dose 4 Gm.—1 teaspoonful of the mixture containing 0.5 Gm. acetarzone. In case of pregnancy, if insufflation is employed care must be taken to exert no positive pressure in the vagina.

Tests and Standards—

Acetarzone is a white, odorless powder, having a slightly acid taste. It is slightly soluble in water and alcohol and readily soluble in solutions of alkalis or alkaline carbonates. It is stable at ordinary temperatures.

To a solution of 1 Gm. of acetarzone in 10 cc. of sodium hydroxide solution and 10 cc. of water, add 2 Gm. of sodium hydrosulfite and warm the mixture to about 50 C. a light yellow precipitate is formed which is soluble in an excess of sodium hydroxide. To a solution of 0.5 Gm. of acetarzone in 10 cc. of water, and a slight excess of ammonia water, add magnesia mixture; no precipitate forms (absence of inorganic arsenates), but on heating the mixture for some time a precipitate is produced. Dissolve 1 Gm. of acetarzone in 10 cc. of

than 0.2 per cent of residue remains. Dry a weighed quantity of acetarzone to constant weight at 100 C. the loss does not exceed 0.5 per cent.

Determine the arsenic of acetarzone by the Lehmann method; the arsenic content corresponds to from 27.1 to 27.4 per cent.

ABBOTT LABORATORIES

Acetarzone (Powder): 4 Gm., 12 Gm., 20 Gm. and 100 Gm.

Tablets Acetarzone 50 mg., 0.1 Gm., and 0.25 Gm.

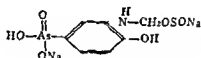
MERCK & Co., Inc

Stovarsol (Acetarzone) (Powder)

Tablet Stovarsol 50 mg 0.1 Gm and 0.25 Gm

U. S. trademark 177 082

PHENARSONE SULFOXYLATE—Aldarzone—Sodium 3-amino-4-hydroxyphenylarsonate N-methanal sulfoxylate—Phenarzone sulfoxylate consists chiefly of the sodium salt of the pentavalent arsenical compound 3-N-methanal sulfoxylic acid amino-4-hydroxy-phenylarsonic acid admixed with minor amounts of sodium chloride and sodium bicarbonate incidental to its manufacture. It contains from 17.0 to 18.5 per cent of arsenic requirements for Public Health the arsenical



Actions and Uses—Phenarzone sulfoxylate, a pentavalent

oxylate is a pentavalent arsenic compound every care should be exercised and visual and color field examinations made prior to drug therapy so that contraction of visual field or symptoms of blurring may be observed.

Dosage—For the treatment of central nervous system syphilis 1 Gm of phenarzone sulfoxylate dissolved in 10 cc of sterile distilled water, administered intravenously once a week. The injections may be given continuously for periods of forty to fifty weeks. Concurrent bismuth therapy may be employed during a portion of the course of phenarzone sulfoxylate injection. Phenarzone sulfoxylate may be given as a supplement to fever therapy in the treatment of various forms of central nervous system syphilis.

For the treatment of *Trichomonas vaginalis* phenarzone sulfoxylate may be administered by insufflation of the powder (with kaolin) and in the form of a suppository. For insufflation the vaginal tract and external os of the cervix are thoroughly cleansed and dried; then the contents of a 3 Gm vial of phenarzone sulfoxylate with kaolin are introduced by an insufflator. A cautionary statement is issued on the use of positive pressure in the pregnant female when insufflation is

employed. The escape of air from the vagina should be permitted during compressions in case the patient is pregnant. The patient is treated for three consecutive days. Then additional treatments are given at three day intervals. No douche should be taken during the treatment.

Phenarsone sulfoxylate suppositories may be used in conjunction with insufflation. They offer a way of providing phenarsone sulfoxylate between insufflation treatments. Suppository treatment is started no sooner than twenty four hours after the last power treatment. One is inserted every second or third night until the patient reports for the next insufflation treatment. They may also be used alone by insertion of one suppository every third or fourth night for not more than three weeks. The patient should be warned against prolonged use of this treatment without the advice of a physician, since an arsenical is being employed. Suppositories alone should not be expected to produce permanent results merely to lessen the discharge and diminish symptoms.

Tests and Standards—

Phenarsone sulfoxylate occurs as a white odorless amorphous powder. It is soluble in water, dilute acids, alkalis and alkali carbonates, slightly soluble in methyl alcohol and insoluble in ether and ethyl alcohol. The pH of a 5 per cent solution is from 7.0 to 7.4.

alcohol. The pH of a 5 per cent solution is from 7.0 to 7.4.

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1. *Journal of the American Medical Association*, 1997; 278: 1039-1044.

1. *Journal of the American Medical Association*, 1997; 278: 1039-1044.

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1. *Journal of the American Medical Association*, 1997; 277: 1039-1043.

1031. 0781 adding 0.48 part of sodium bicarbonate. no color develops in

the chloroform layer, but the aqueous layer is colored light brown.

Add 2 cc of diluted nitric acid and 1 cc of silver nitrate solution to

5 cc. of a 1 per cent solution of phenarsonc sulfoxylate a black

precipitate forms, heat to boiling and cool the mixture rapidly

changes to a yellow brown solution containing a white precipitate
decant the solution, the precipitate is soluble in excess ammonia

Add 3 drops of alkaline potassium mercuric iodide solution to 5 cc

of a 1 per cent solution of phenarsona sulfoxylate a gray to black

precipitate of metallic mercury is formed (distinction from acetarsone

| tryparamide and other pentavalent arsenicals) | |

Dissolve 0.1 Gm of phenarsonesulfoxylate in 5 cc of water, add

water and 1.55 of a

ent sodium

• • • • • J amino-4

■ ■ ■

[illegible]

occasional forms (absence of anisomeric exocyclic). Heat the solution

precipitate forms (insoluble by inorganic analysis) Heat the solution to boiling a white precipitate forms slowly

Dry an accurately weighed 1 Gm portion of phenarsone sulfoxylate

contained in a weighing bottle not less than 20 mm diameter over

fresh phosphorus pentoxide for twenty four hours in a vacuum of at least 10^{-4} mm. The phosphorus pentoxide must not be more than 25 per

least 5 mm of mercury the loss in weight is not more than 2.5 per cent. Transfer about 0.5 Gm. of phenazone sulfonate accurately

weighed to a tared porcelain dish, add 0.5 cc. of sulfuric acid and

Cool treat the ash with 5 drops of sulfuric acid and 5

Evaporate the acids over a low flame

and then ignite cool and weigh the weight of the sulfated residue

is equivalent to sodium content of not less than 15.2 per cent nor more than 16.2 per cent. The residue responds to tests for sodium.

Dissolve about 0.5 Gm. of phenarsone sulfoxylate accurately weighed in 25 cc. of water, add 10 cc. of silver nitrate solution and 10 cc. of nitric acid. Warm on a steam bath for fifteen minutes and finally add 100 cc. of water. Continue the digestion on the steam bath for thirty minutes, cool, allow to stand thirty minutes and collect the precipitated silver chloride on a suitable tared sintered glass filter (or Gooch crucible). Wash the precipitate and dry at 100 C. for one hour. The weight of silver chloride found is equivalent to a chlorine content of not less than 6.5 per cent nor more than 7.5 per cent.

Dissolve about 0.5 Gm. of phenarsone sulfoxylate in 10 cc. of water contained in a 400 cc. beaker and add a solution made by dissolving carefully 5 Gm. of sodium peroxide in 25 cc. of water. Cover the beaker with a watch glass and heat on a steam bath for one hour. Cool, add hydrochloric acid down the side of the beaker with stirring until the solution is colorless and then add 1 cc. in excess. Add 25 cc. of water and boil the solution gently covering the beaker with a watch glass until the volume is reduced by one half. Dilute to approximately 300 cc. with water, boil and add 15 cc. of barium chloride solution dropwise at first until a precipitate forms. Digest the mixture for one hour on the steam bath and filter while hot, collecting the precipitated barium sulfate on a suitable tared previously ignited Gooch crucible. Wash the precipitate with hot water until chlorides are absent from the washings. Dry the crucible and contents at 100 C. for fifteen minutes and finally ignite at 650 C. for fifteen minutes. The weight of barium sulfate formed is equivalent to a sulfur content of not less than 6.5 per cent nor more than 7.5 per cent.

Transfer about 0.5 Gm. of phenarsone sulfoxylate accurately weighed to a 250 cc. wide mouthed Erlenmeyer flask, add 10 cc. of water to dissolve the sample taken and then add 15 cc. of 30 per cent hydrogen peroxide. Mix and add 10 cc. of sulfuric acid slowly down the side of the flask, shaking the mixture after each addition. Place a short stemmed funnel in the top of the flask and heat at medium temperature until the reaction subsides. Remove the funnel and heat for twenty minutes at a temperature such as to produce sulfur trioxide fumes freely. (If at the end of five minutes the solution is not colorless, cool and add from 2 to 5 cc. of 30 per cent hydrogen peroxide then continue to heat as before.) Cool and add through a long stemmed funnel 0.2 Gm. of hydrazine sulfate (chlorine free). (Care should be taken to avoid contact of the hydrazine solution with the neck of the flask.)

zinc sulfate and sulfur trioxide from the top of the flask for twenty minutes. Cool and dilute (carefully) with 20 cc. of distilled water, add from 3 to 5 drops of a methyl orange solution (3 cc. of methyl orange test solution diluted to 100 cc. with water) and titrate while hot with tenth normal potassium bromate solution until the solution becomes colorless. Near the end point the potassium bromate solution should be added dropwise. Each 1 cc. of tenth normal potassium bromate is equivalent to 0.003746 Gm. of arsenic. The amount of arsenic found is not less than 17.0 per cent nor more than 18.5 per cent.

ABBOTT LABORATORIES

Aldarsone (Powder) Phenarsone sulfoxylate 0.5 Gm. and 1 Gm. ampuls

Aldarsone Vaginal Suppositories Each suppository contains phenarsone sulfoxylate 0.13 Gm. in a glycerogelatin base

Aldarsone with Kaolin 30 Gm. Each 30 Gm. contains phenarsone sulfoxylate 0.5 Gm. and kaolin 2.5 Gm. packaged in glass tubes suitable for use with insufflator

U S Pat No 2 074 757 U S Trademark 338 986

CARBARSONE—'When dried at 80° C for six hours, contains from 281 to 288 per cent arsenic (As)' U S P



For description and standards see the U S Pharmacopeia under Carbarsone.

Actions and Uses—Carbarsone is proposed for the treatment of intestinal amebiasis. It is administered usually by mouth, in acute amebic dysentery or in resistant cases with motile amebas in the stools, retention enemas may be employed. While carbarsone is said to be less toxic than acetarsone and serious untoward effects appear to be uncommon, cutaneous disturbances and other reactions common to arsenic compounds have

possibility of their occurrence should nevertheless be kept in mind during the therapeutic use of the drug. A moderate increase in intestinal activity may be observed. Carbarsone in common with other arsenicals, should ordinarily not be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow, suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa, positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

Dosage—Orally for adults the usual dose is 0.25 Gm. twice a day for ten days, a ten day rest period according to weight of the drug dissolve bicarbonate solution may be administered following a cleansing

alkaline enema every other night for a maximum of five doses if necessary. Because of the large dosage employed (a total of 10 Gm over a period of nine days) oral administration should be interrupted during this interval.

ELI LILLY AND COMPANY

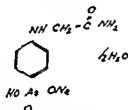
Carbarsone (Powder) 2 Gm vial

Pulvules Carbarsone 0.25 Gm

Suppositories Carbarsone* 0.12 Gm

Tablets Carbarsone 50 mg and 0.25 Gm

TRYPARSAMIDE—When dried to constant weight at 110° C contains not less than 25.1 per cent and not more than 25.5 per cent of arsenic (As) *U S P*



For description and standards see the U S Pharmacopeia under Tryparsamide

Actions and Uses—Tryparsamide was first used as a trypanocidal agent especially in the treatment of trypanosomiasis due to *T. gambiense* but is now used as well in resistant cases of syphilis of the central nervous system.

Tryparsamide has some spirocheticidal activity and has an unusual power of therapeutic penetration especially in case of the central nervous system. The best results seem to have been obtained in patients with early dementia paralytica. It is estimated that perhaps from 40 to 50 per cent of such cases

deterioration have shown little or no improvement. On the other hand the drug may hasten the progress of the disease in such cases. Its use is considered inadvisable in forms of syphilis other than that of the central nervous system. It is being used quite extensively as the follow up treatment after malaria therapy in syphilis of the central nervous system.

The toxic effects of tryparsamide resemble those of other pentavalent arsenic compounds. The worst of these is the tendency to produce amblyopia but cases of nitritoid reactions of jaundice of agranulocytosis and of toxic hepatitis have also

been reported. Before using the drug, careful consideration should be given to the frequent production of visual injury, which may be serious and permanent. This caution is especially important if the neurosyphilis has involved the optic nerve, causing contraction of the visual and color fields. The drug is, of course, contraindicated in conditions characterized by such contraction. The eyeground fields including color fields, should always be mapped out before its use is undertaken and should be checked several times thereafter. Sometimes after one or two injections the patient will complain of blurred vision for a few days. In such cases treatment with tryparsamide should be discontinued, the visual fields determined at least weekly for three to four weeks, and then if there is no evidence of damage to the optic nerve, the injection resumed using great caution, minimal dosage at first, and checking the visual field preceding each injection. The drug is said to "have no virtues in ophthalmic syphilis."

Dosage—From 10 to 30 Gm for adults, depending on the purpose for which the drug is used. In general, the dose should not exceed 0.04 to 0.05 Gm per kilogram of body weight, and such doses should not be repeated at intervals of less than one week. Tryparsamide is employed by the intravenous route. The drug is dissolved in sterile water or physiologic solution of sodium chloride. Tryparsamide should never be administered by mouth.

MERCK & Co., Inc

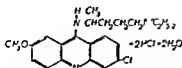
Tryparsamide (Powder) 50 Gm bottle and 1 Gm, 2 Gm and 3 Gm ampuls

U. S. patents 1,280,119, 1,280,120, 1,280,121, 1,280,122, 1,280,123, 1,280,124 and 1,280,126 (Sept. 24, 1918 expired) by license of the Rockefeller Institute for Medical Research. U. S. trademark 186,072.

Quinacrine Compounds

QUINACRINE

Hydrochloride
contains not less than
98 per cent of



For description and standards see the U. S. Pharmacopeia under Quinacrine Hydrochloride and Quinacrine Hydrochloride Tablets.

Actions and Uses—Quinacrine hydrochloride destroys the asexual forms (trophozoites) of the causative organism in all types of malaria and thus checks the progress of the disease. Given during the first paroxysms of a benign tertian (*P. vivax*) attack it will often prevent completely the appearance of the third paroxysm while considerably lessening the severity of the second. At present the consensus is that in ordinary cases of benign type and also in the more rare quartan (*P. malariae*) type it gives as good results as quinine. Some observers are of the opinion that relapses are less frequent than with quinine and that the period of treatment is shorter. Quinacrine hydrochloride is considered by some inferior to by some equal to and by others more effective than quinine in the treatment of malignant subtertian (*P. falciparum*) malaria. It is of value in the treatment of blackwater fever when the treatment of quinine is contra indicated. Like quinine the drug effects partial destruction of the sexual forms (gametocytes) of the malarial organisms and thus lessens in some degree the extent to which the patient may act as a reservoir from which mosquitoes may be infected; this action is however least pronounced in the malignant subtertian form. If taken faithfully in prophylactic dosage quinacrine hydrochloride will reduce the incidence of frank clinical malaria being in this regard perhaps somewhat more effective than quinine.

Quinacrine hydrochloride is reported to be effective in combating *Giardia lamblia* infestation but the evidence that this organism is pathogenic for man or is the cause of diarrhea and other symptoms associated with its presence in the gastrointestinal tract is inconclusive.

Quinacrine hydrochloride causes the urine to become very yellow on the third to fifth day and being of an acridine dye nature it may cause discoloration of the skin the latter persisting usually no longer than two weeks. Headache and relatively mild gastrointestinal symptoms occur but not very frequently. The drug does not cause visual or aural disturbances and may therefore be preferred to quinine by patients who have experienced both drugs. The circulatory system does not seem to be disturbed by quinacrine hydrochloride in therapeutic dosage. The drug is not considered to be toxic to the liver or kidneys. Some patients claim to be stimulated by quinacrine hydrochloride. A relatively small number of psychotic attacks have been attributed to the drug—some quite severe—but no permanent derangements have been recorded. Apparently the drug may be used with safety in any stage of pregnancy though many observers withhold it in toxemia.

Quinacrine hydrochloride is absorbed readily from the intestine and is excreted slowly in the urine and feces. It is usually given by mouth but may also be given intravenously or intramuscularly the latter route being preferred if injection must be resorted to at all.

Dosage—

Therapeutic Dose for clinical malaria Adults 2 tablets of 0.1 Gm each and sodium bicarbonate 1 Gm by mouth with 200 to 300 cc of water (or an equal amount of sweetened tea or fruit juice) every six hours for 5 doses then 1 tablet of 0.1 Gm 3 times daily for 6 days

Children 1 to 4 years 1 tablet of 0.1 Gm 3 times daily for the first day then 1 tablet of 0.1 Gm once daily for 6 days

Children 4 to 8 years 2 tablets of 0.1 Gm 3 times daily for the first day then 1 tablet of 0.1 Gm twice daily for 6 days

Over 8 years Same as adults

Suppressive Dose in malarious areas Adults 1 tablet of 0.1 Gm daily preferably beginning two weeks in advance of exposure and continuing for at least four weeks after last possible exposure in a malarious area

Children 1 tablet of 50 mg daily

Suppressive Dose in persons who have had attacks of vivax malaria within 6 months and no quinine (atabrine) for 3 weeks

Adults 1 tablet of 0.1 Gm 3 times a day for 3 days then 1 tablet of 0.1 Gm daily

Children 1 tablet of 50 mg 3 times a day for 3 days then 1 tablet of 50 mg daily

Note Each dose therapeutic or suppressive should be taken with a full glass of water after a meal

The technic of the intramuscular or intravenous administration must be learned before the method is used. Details will be found in the circulars of manufacturers and in various publications

WINTHROP CHEMICAL COMPANY, INC

Atabrine di-Hydrochloride Powder 0.2 Gm ampuls packaged with 10 cc ampuls of sterile distilled water

Tablets Atabrine di-Hydrochloride 50 mg and 0.1 Gm (plain) and 0.1 Gm (sugar coated)

U. S. patent 2,113,357 (Apr 15, 1938 expires 1953) U. S. trademark 302,473

Bismuth Compounds

Until 1921 bismuth had been used particularly in the treatment of intestinal infections as a paste for tuberculous fistulae and in radiology. Satter and Robert then showed the value of sodium potassium bismuth tartrate in trypanosomiasis and spirillosis of fowls. Sazerac and Levaditi then took up the treatment of syphilis with the same drug. From that time on the value of bismuth preparations for treating syphilis has

been more and more realized and its general use has been increased enormously throughout the world. Bismuth seems to have both a spirocheticidal and a spirochetostatic effect.

For use in the treatment of syphilis, the administration of the greater number of this type of bismuth preparations by the mouth has not proved satisfactory nor has the value of bismuth inunctions been shown. Thus far the best results with bismuth therapy of syphilis have been achieved by intramuscular injections. Probably those compounds of bismuth will have the best spirocheticidal value that are able to keep the therapeutic level of bismuth in the blood stream at such a continuous height that it will be reflected in the urine with a level of 0.002 Gm. or more of metallic bismuth per day. Intravenous injections are strictly contraindicated for the reason that the therapeutic dose approaches too closely to the toxic dose. The compounds employed for intramuscular injection consist of water soluble salts dissolved in aqueous solution or other suitable solvents or suspended in oils of insoluble bismuth salts suspended in water or oils, of so called oil soluble preparations, of water soluble and oil suspended combinations and finally of bismuth and arsenic compounds. The so called oil soluble preparations are claimed to be more exact in their dosage than insoluble suspensions of bismuth salts. They are said not to be absorbed and excreted so rapidly as the soluble bismuth preparations. Yet the claim is made that they are absorbed more rapidly than the insoluble bismuth salts in suspension. Thus the claim is made that they combine some of the advantages of both the soluble and of the insoluble preparations. This question has not been entirely and satisfactorily answered as yet. Thus far it seems to be the generally accepted opinion that bismuth salts used in the treatment of syphilis should be administered by the intramuscular route. In intramuscular injections of the bismuth salts the needle should be inserted in the upper and outer quadrant of the gluteal region near the inner angle of the quadrant. Having the syringe tip firmly inserted into the butt of the needle the physician should hold the syringe loosely between the thumb and first finger, much like holding a pencil. The skin of the buttock is drawn down a little with the left hand and then with a free back and then forward motion of the right hand the needle (pointed upward and slightly toward the median plane at an angle of about 70° with the skin) is boldly plunged not pushed deep into the muscular tissue. With the needle still in place the physician should then aspirate back with the plunger of the syringe several times in order to be sure that the needle is not in a vein or in an artery. This having been ascertained the needle butt is held firmly in place with the thumb and first finger of the left hand while the injection is made with the right hand. This will go far toward obviating many of the distressing venous emboli

and arterial emboli that have been reported. Those who have worked with bismuth salts in treating syphilis believe that their efficiency stands between that of mercury and that of arsphenamine. The present evidence appears to show that there is warrant for the administration of bismuth compounds in the treatment of syphilis in connection with arsphenamine or as a substitute for mercury therapy. Some few syphilologists use bismuth therapy alone in treatment of syphilis. These men are much in the minority, however. Bismuth compounds are most valuable in the treatment of syphilis in patients who are intolerant to other drugs or who show resistance to other drugs used in syphilis.

ment with bismuth preparations is not usually injurious if the necessary precautions are taken (careful observation of the skin for untoward reaction, of the mouth for signs of beginning bismuth stomatitis and of the urine for evidence of irritation of the kidneys).

Until the controversy concerning the penetration of appreciable amounts of special bismuth salts into the tissues of the central nervous system and of their presence in the spinal fluid is settled by more convincing evidence, it appears unwise to accept therapeutic implications based on such claims.

In common with another heavy metal, mercury, bismuth preparations when administered by injection, have a definite diuretic action. Excretion studies of various bismuth compounds used in the treatment of syphilis give some indications as to the best type of bismuth salts for desired results. The usefulness of a bismuth preparation involves the concentration of active bismuth attained in the tissues especially in the blood, and the height, course, rise, duration and decline of this concentration. As a rule, watery solutions if repeated

is a slower absorption and concentration in the blood stream, but one which persists longer, thus requiring injections but once a week. Certain of the oil solutions have like characteristics with an added more rapid absorption than the oil suspensions. Bismuth subsalicylate is more slowly absorbed and there is a somewhat longer delay before the bismuth effect is achieved. Moreover, in small amounts it continues to be excreted over long periods of time even months after injections are stopped. Whether this long excretion indicates a therapeutic level of the drug in the body is doubtful.

BISMO-CYMOL—A basic bismuth salt of camphocarboxylic acid (camphor-3 carboxylic acid) having the probable formula $(C_{10}H_{15}O_2COO)_2BiOBi(C_{10}H_{15}O_2COO)OH$. It contains between 37 and 40 per cent of bismuth.

Actions and Uses—Bismo cymol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds). Bismo cymol belongs to the compounds which, because rapidly than insoluble bismuth salts. Though animal experiments seem to show a low toxicity for this preparation in human beings it is well to watch the gums closely for evidence of beginning stomatitis.

Dosage—Bismo-cymol is injected intramuscularly in doses representing 0.1 Gm of metallic bismuth once a week or in doses representing 50 mg of metallic bismuth twice a week for from eight to ten weeks.

Tests and Standards—

Bismo-cymol occurs as a white powder having the odor of camphor. It is insoluble in water but soluble in ether, benzene and vegetable oils.

Heat 1 Gm of bismo cymol in 30 cc of water containing 3 cc of hydrochloric acid, add ammonia water until resulting solution is alkaline to litmus, filter and wash the precipitate with 7 cc of water, to the filtrate add hydrochloric acid until just acid to litmus, evaporate on the steam bath until the volume is reduced one half, cool, filter and dry the crystals, the crystals melt at 127°C. Dissolve 0.1 Gm of the crystals in 5 cc of alcohol, add a drop of diluted ferric chloride solution (ferric chloride solution diluted 1 to 5), a green color results. Dissolve the precipitate (obtained from the treatment with ammonia water) in diluted hydrochloric acid and pass in hydrogen sulfide, a black precipitate forms. Suspend 0.2 Gm of bismo cymol in 10 cc of boiling water and add 2 Gm of sodium hydrosulfite, a black precipitate forms.

Add 5 cc of sodium hydroxide solution and about 0.2 Gm of aluminum wire to about 0.2 Gm of bismo-cymol, heat gently, the vapors do not turn red litmus blue (nitrate). Suspend 0.25 Gm in 30 cc. of water, add 4 cc diluted nitric acid, boil, cool, filter and add 1 cc of silver nitrate solution, no more turbidity is produced than in the U. S. P. test for chlorides using 0.1 cc of fiftieth normal hydrochloric acid (chloride). Suspend 0.1 Gm in 30 cc of water, add 4 cc of diluted hydrochloric acid, boil, cool, filter, add 1 cc of barium chloride solution and dilute to 50 cc, no turbidity is produced in ten minutes (sulfate). Add 2 cc of nitric acid to 2 Gm of bismo cymol

water, evaporate to 30 cc. Add 1 cc of 10% sodium hydroxide solution, quite n of rken rartz the lled

portions. To one portion add an equal quantity of diluted sulfuric acid, the liquid does not become cloudy (lead). To another portion add an excess of ammonia water, the liquid does not exhibit a bluish tint (copper). To another portion add 0.5 cc of diluted hydrochloric acid, a precipitate insoluble in an excess of hydrochloric acid and soluble in ammonia water is not formed (silver).

Transfer about 0.2 Gm of bismo-cymol accurately weighed to an Erlenmeyer flask, add 1 Gm of powdered potassium permanganate and then 5 cc of diluted sulfuric acid, allow to stand ten minutes.

add 10 cc of sulfuric acid in small portions, allow to stand fifteen minutes decolorize with hydrogen peroxide add 25 cc of water boil for fifteen minutes, pass in hydrogen sulfide until the bismuth is completely precipitated filter through a prepared Gooch crucible wash with water alcohol chloroform and ether in this order, dry in an oven for thirty minutes at 100 C., cool in a desiccator and weigh repeat the washing with chloroform and ether and the drying at 100 C until constant weight is attained The weight of bismuth sulfide corresponds to not less than 32 nor more than 40 per cent bismuth

ABBOTT LABORATORIES

Solution Bismo-Cymol: 1 cc and 2 cc ampuls and 60 cc and 500 cc bottles. Each cc contains bismo cymol equivalent to 50 mg of metallic bismuth, dissolved in olive oil.

U S patent 1,921 638 (Aug 8, 1933, expires 1950) U S trade
mark 277,960

BISMOSOL—A sterilized solution of potassium sodium bismuthotartrate (containing 35 per cent bismuth [Bi]) 10 Gm, piperazine, 0.3 Gm., in an aqueous solution of glucose, to make 100 cc Preserved with 0.1 mg n butyl parahydroxybenzoate

Actions and Uses—Bismosol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds).

Dosage—Bismosol is administered intramuscularly in doses of 1 cc every two days until twenty doses have been given. After an intermission of one month, a second course may be given.

Tests and Standards—

The authors are grateful to the National Science Foundation for support of this work under Grant Number NSF-44409.

solution of hydrogen peroxide one drop of ferrous sulfate solution and then an excess of sodium hydroxide solution a purple violet color is produced. To 1 cc bismosal add diluted hydrochloric acid drop by drop, until the precipitate which is formed has red solved and then add a few cubic centimeters of potassium bismuth iodide solution a brilliant red precipitate is produced.

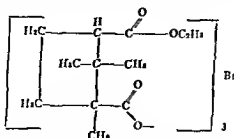
To 5 cc of bismolol add about 100 cc water and sufficient hydrochloric acid to redissolve the precipitate first formed, heat the solution to from 70 to 80 C. and saturate with hydrogen sulfide to precipitate completely the bismuth as bismuth sulfide. Collect the bismuth sulfide on a tared Gooch crucible, wash successively with water, alcohol, carbon disulfide and alcohol dry to constant weight at 110 C. The weight of bismuth sulfide is equivalent to 3.5 Gm of bismuth (Bi) in 100 cc of bismolol.

MEYER & Co., Inc.

Solution Blismosol: 1 cc ampule

U. S. trademark 196 017

BISMUTH ETHYLCAMPHORATE—The bismuth III salt of *d* camphoric acid mono ethyl ester. It possesses the following formula



$[\text{C}_{12}\text{H}_{18}\text{O}_4]_3\text{Bi}$ —M W 890.8 It may be prepared by the interaction of sodium ethylcamphorate and bismuth nitrate in dilute aqueous glycerin solution. The product may then be extracted with chloroform and recovered by the removal of that solvent.

Actions and Uses—Bismuth Ethylcamphorate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis. It is a liposoluble compound not so readily absorbed as the water soluble preparation and yet more rapidly absorbed than the suspensions of insoluble bismuth salts in oil. Injection intramuscularly of this preparation produces relatively little local reaction.

Dosage—For the average adult 2 cc (80 mg of metallic bismuth), administered once a week for a series of ten to fifteen injections.

Tests and Standards—

Bismuth ethylcamphorate giving a faint aromatic odor in chloroform, ether, ethylene bility in the latter is increased ethylcamphorate softens at about 55 C and melts indefinitely between 61 and 67 C.

Dissolve about 0.25 Gm of ether in a separator, add dilute the white precipitate which is then separate and wash the eth acid layer responds to tests for with 25 cc portions of sodium bined alkaline extracts in a beaker the beaker with a watch glass and continue to heat for about two hours, filter, cool and acidify the solution with diluted sulfuric acid and allow the precipitate to crystallize. Separate and recrystallize the product from a small amount of hot water. The melting point of the dried *d* camphoric acid obtained is from 166 to 188 C.

Place 0.25 Gm of bismuth ethylcamphorate accurately weighed in a tared wide dish heat at 75-80 C under pressure of 10 to 15 mm of mercury to constant weight the loss in weight is not more than 2.5 per cent.

Transfer about 0.5 Gm of bismuth ethylcamphorate accurately weighed to a 500 cc Kjeldahl flask add 15 cc of sulfuric acid and

of hydrochloric acid and soluble in ammonia water is not formed (silver) Ignite 1 Gm in a quartz crucible The residue meets the requirements of Bettendorf's test U S P X, p 430 (arsenic)

Dry about 1 Gm of sodium bismuth tartrate weighed accurately at 100 C to constant weight the loss is from 2.6 to 3.6 per cent Dissolve about 0.5 Gm in 20 to 30 cc of water weigh to redissolve the precipitate for sulfide, collect the precipitate, wash with water, alcohol, and dry at 100 C more than 73.9 per cent

G D SEARLE & Co

Solution Bismuth Sodium Tartrate, 1.5 per Cent 2 cc ampul and 60 cc vial An aqueous solution containing bismuth sodium tartrate 30 mg benzyl alcohol 40 mg and sucrose 0.50 Gm, in 2 cc

Solution Bismuth Sodium Tartrate, 3 per Cent 2 cc ampuls and 60 cc vial An aqueous solution containing bismuth sodium tartrate 30 mg, benzyl alcohol 20 mg and sucrose 0.25 Gm, in one cubic centimeter

U S patents 1 663 201 (March 20 1928, expired) and 1 801 433 (April 21 1931 expires 1948)

BISMUTH AND POTASSIUM TARTRATE—Potassium Bismuth Tartrate—Potassium Bismuthyl Tartrate—A basic bismuth potassium bismuthotartrate, containing the equivalent of not less than 60 per cent and not more than 64 per cent of bismuth (Bi) U S P

For description and standards see the U S Pharmacopeia under Bismuth and Potassium Tartrate and Bismuth and Potassium Tartrate Injection

Dosage—(a) *Oily Suspension*—From 0.1 to 0.2 Gm by intramuscular injection, preferably into the gluteal muscle The injections may be repeated at intervals of seven days until a total of from 24 to 30 Gm has been given (b) *Aqueous Isotonic Solution*—50 mg by intramuscular injection preferably into the gluteal muscles three times a week until a total of 12 to 18 injections has been given

ABBOTT LABORATORIES

Potassium Bismuth Tartrate (Aqueous) 2 cc ampuls Each ampul contains potassium bismuth tartrate 50 mg (equivalent to 31 mg elemental bismuth) in an aqueous solution containing benzyl alcohol 2 per cent and sucrose 6 per cent

Suspension Potassium Bismuth Tartrate with Butyn 2 cc ampuls Each ampul contains potassium bismuth tartrate, 0.2 Gm and butyn 0.4 per cent with metaphen 1:20 000 suspended in peanut oil

Potassium Bismuth Tartrate (Aqueous) 2.5 per Cent—(6 cc. bottle) Potassium bismuth tartrate, 2.5 per cent in an aqueous solution containing benzyl alcohol 2 per cent, and sucrose 6 per cent.

Potassium Bismuth Tartrate in Oil 10 per Cent with Butyn—(6 cc. bottle) Each cc. contains potassium bismuth tartrate 0.1 Gm. (equivalent to 62 mg. elemental bismuth), butyn 0.4 per cent and metaphen 1:20000 suspended in peanut oil.

Wick & Co., Inc.

Bismuth and Potassium Tartrate (Powder)* 1%.

BISMUTH SUBSALICYLATE—*Pharm. Bismuth Salicylate*.—"A basic salt, which when dried over sulfuric acid for 18 hours yields upon ignition not less than 62 per cent and not more than 66 per cent of Bi_2O_3 ." U. S. P.

For description and standards see the U. S. Pharmacopoeia under Bismuth Salicylate and Bismuth Salicylate Injection.

ARTOTT LABORATORIES

Bismuth Subsalicylate with Butyn in Oil—30 cc., 60 cc., and 120 cc. bottles. A 10 per cent suspension of bismuth subsalicylate in peanut oil to which has been added 0.4 per cent of butyn base and metaphen 1:20000. Each cubic centimeter contains 57 mg. of elemental bismuth.

Bismuth Subsalicylate with Butyn in Oil—1 cc. ampule. A 10 per cent suspension of bismuth subsalicylate in peanut oil to which has been added 0.4 per cent of butyn base and metaphen 1:20000. Each cubic centimeter contains 57 mg. of elemental bismuth.

BAXTER LABORATORIES, INC.

Bismuth Subsalicylate in Oil with Chlorobutanol 3%. 0.13 Gm. in 1 cc. ampule. A suspension of bismuth subsalicylate in oil containing 3 per cent of chlorobutanol. Each cubic centimeter 0.13 Gm. of bismuth subsalicylate and 3.9 Gm. of chlorobutanol 3 per cent.

Bismuth Subsalicylate in Oil with Chlorobutanol 3%. Ampule 1 cc., 2 cc., and 4 cc. bottles. A suspension of bismuth subsalicylate in oil containing 3 per cent of chlorobutanol. Each cubic centimeter 0.13 Gm. of bismuth subsalicylate and 3.9 Gm. of chlorobutanol 3 per cent.

ELDER & DE WESSCHER & Co., Inc.

Hypocystyl Bismuth Subsalicylate in Oil with Chlorobutanol 3%. 0.13 Gm. in 1 cc. ampule. A suspension of

bismuth subsalicylate in peanut oil containing in each cubic centimeter bismuth subsalicylate 0.13 Gm with 3 per cent chlorobutanol

DIARSENOL COMPANY, INC

Bismuth Subsalicylate in Oil with Chlorobutanol 3%, 30 cc, 60 cc, and 100 cc bottles. A suspension of bismuth subsalicylate in peanut oil each cubic centimeter containing 0.13 Gm of bismuth subsalicylate (equivalent to 75 mg of Bi metal) and 30 mg (3 per cent) of chlorobutanol.

THE DRUG PRODUCTS CO., INC

Bismuth Subsalicylate with Chlorobutanol 3%, in Oil 60 cc hypodermics. This multiple dose vial contains in each cubic centimeter bismuth subsalicylate 0.13 Gm chlorobutanol anhydrous 30 mg and olive oil q. s.

ENDO PRODUCTS, INC

Bismuth Subsalicylate in Oil with Chlorobutanol 3%, 2 cc ampuls. A suspension of bismuth subsalicylate in peanut oil containing in each cubic centimeter bismuth subsalicylate U. S. P. equivalent to 50 milligrams to 60 milligrams of bismuth with 3 per cent of chlorobutanol.

Bismuth Subsalicylate in Oil with Chlorobutanol 3%, 20 cc, 60 cc and 100 cc bottles. A suspension of bismuth subsalicylate in peanut oil containing in each cubic centimeter bismuth subsalicylate U. S. P. equivalent to 50 milligrams to 60 milligrams of bismuth with 3 per cent chlorobutanol.

MENCK & CO. INC

Bismuth Subsalicylate (Powder) bulk.

PARKE, DAVIS & COMPANY

Bismuth Salicylate in Oil with Chloretone 3%, 30 cc, 60 cc and 500 cc bottles. ^a in peanut oil containing cubic centimeter contains b.

Bismuth Salicylate in Oil with Chloretone 3%, 0.13 Gm in 1 cc ampuls. Each ampul contains 1 cc of a suspension of bismuth subsalicylate 0.13 Gm in peanut oil containing 3 per cent of chlorobutanol.

SHARP & DOHME INC

Bismuth Subsalicylate with Chlorobutanol 3%, in Oil 0.13 Gm in 1 cc ampuls. Each cubic centimeter contains bismuth subsalicylate 0.13 Gm and chlorobutanol 30 mg suspended in peanut oil.

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SODIUM IODOBISMUTHITE AND PROPYLENE GLYCOL. The sodium iodobismuthite and propylene glycol in iodobismutol with benzocaine conform to the New and Nonofficial Remedies standards for these substances.

BENZOCAINE. The benzocaine in iodobismutol with benzocaine conforms to the U S P standards for this substance.

E. R. SQUINN & SONS

Solution Iod
50 cc rubber ca
bismuthite 0.12 .
propylene glycol q s 2 cc

QUININE BISMUTH IODIDE—A substance of variable composition containing between 18 and 20.1 per cent of bismuth, between 48.7 and 53.5 per cent of iodine, and quinine.

Actions and Uses—Quinine bismuth iodide is proposed as a means of obtaining the systemic effect of bismuth in the treatment of syphilis (See preceding article, Bismuth Compounds).

Tests and Standards—

Quinine bismuth iodide is a red powder that clings to most surfaces.

nitric acid the material dissolves and a brown or blackish colored vapors are given off.

(iodides)

Shake 0.75 Gm of quinine bismuth iodide with 4 cc of potassium iodide solution filter, add 1 cc of chloroform to the filtrate shake and allow to stand five minutes the chloroform does not acquire a purple tinge (iodine).

weighed
sulfuric
weight
600 cc
1 cc of
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plutonium
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ash ignite in a weighed quartz crucible add a few drops of nitric acid, evaporate and ignite to constant weight, cool in a desiccator and weigh the bismuth oxide weighed is equivalent to not less than 18 per cent nor more than 20.08 per cent of bismuth. Transfer about 0.12 Gm of the original accurately weighed, to a glass capsule, transfer this tube to a Carius tube containing 30 cc of nitric acid and 0.2 Gm of silver nitrate seal and heat for seven hours at 210 C., cool open the tube transfer the contents to a large beaker and dilute to 500 cc. allow to stand for four hours filter through a Gooch cru

cible wash with very dilute nitric acid (1 cc diluted nitric acid in 50 cc of water) dry at 100 C cool in a desiccator and weigh the silver iodide is equivalent to not less than 48.75 per cent iodine more than 53.5 per cent iodine

SOBISMINOL MASS—A complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by the interaction of sodium bismuthate, triisopropanolamine and propylene glycol. It contains between 19.25 and 20.25 per cent of bismuth, 0.75 Gm of sobisminol mass represents 150 mg of bismuth.

Actions and Uses—Sobisminol mass is proposed in the treatment of syphilis and is intended for use by the oral route. It is to be administered by the oral route to undergo absorption by that route. It is to be administered by the oral route to undergo absorption by that route. It is to be administered by the oral route to undergo absorption by that route. Again it may be indicated in certain other types of syphilis e.g. congenital and latent syphilis. It is to be emphasized that it is too dangerous a drug to be employed by the patient without the careful supervision and direction of his physician and it is sold only on prescription. In the first few days of therapy the patient should be carefully supervised and later watched for evidence of gastrointestinal

or solution) appears to be an effective antisyphilitic level. An adequate amount of sobisminol mass by mouth can be expected to result in a curve for urinary excretion resembling closely in course and degree those given by intramuscular injection of the water soluble and oil soluble compounds. The oral dose has to be considerably higher than the intramuscular dose of sobisminol. Further

The toxicity of sobisminol compares favorably with that of other water soluble bismuth compounds used in the treatment of syphilis. Side effects appear to be usually of a relatively transient nature. They include nausea, vomiting, burning sensations in the esophagus, diarrhea, stomatitis and bismuth line. There appears to be no tendency to cumulative toxic effects.

Dosage—Adult dosage from two to three capsules three times a day, taken with plenty of water at 10 a.m., 3 p.m. and 8 p.m. Each capsule represents 150 mg of metallic bismuth. Unless contraindications arise such therapy may be continued for from ten to twelve weeks and represents a course of bismuth therapy. For children the dosage may be cut down to one capsule three times a day, or a 75 mg capsule three times a day for a young child.

Tests and Standards.

Sobisminol mass occurs as a red brown to chocolate brown colored pasty mass, bitter taste, and alcohol solution made by water to malmined with a glass electrode

Dissolve 1 Gm of sobisminol mass in 10 cc. of water and half the solution, to one portion add 5 cc. of 0.5 per cent sodium bicarbonate solution, to the other portion add 5 cc of 0.1 per cent hydrochloric acid neither solution yields a precipitate within fifteen minutes

Dissolve 2 Gm of sobisminol mass in 100 cc. of water, boil a 5 cc portion the solution remains clear and unchanged To a separate portion of 1 cc. add 10 cc. of water and 1 cc. of 5 per cent sodium iodide solution the solution remains clear To another 1 cc portion add 1 cc. of diluted hydrochloric acid, 5 cc of water and 5 cc of hydrogen sulfide solution a black precipitate forms, to another 1 cc portion add 3 cc of diluted sulfuric acid and 1 cc. of 5 per cent sodium iodide solution a red precipitate forms To a 20 cc portion add 2 cc of nitric acid, adding more nitric acid dropwise, if necessary, until the solution is clear, divide into two equal parts, retain one part as a control and add 2 cc. of silver nitrate solution to the other part when compared with the control, not more than a trace of turbidity is apparent (*chloride*) To another 20 cc. portion add 2 cc of hydrochloric acid, adding more hydrochloric acid dropwise, if necessary, until the solution is clear, divide into two equal parts retain one part as a control and add 2 cc. of barium chloride solution to the other part when compared with the control not more than a trace of turbidity is apparent (*sulfate*)

Transfer about 50 Gm of sobisminol mass accurately weighed, to a 100 cc volumetric flask, add water to the mark and shake the contents thoroughly Determine the nitrogen content of an accurately measured 10 cc portion according to the method described in Methods

Agricultural Chemists fourth procedure add 0.1 Gm of the digestion for a period of the amount in acid. After to 50 cc of 10 per cent

ammonium phosphate solution, dilute to a volume of about 400 cc with boiling water and allow the mixture to stand for one hour at 80 C Collect the precipitate on a tared Gooch crucible by first filtering the supernatant liquid then wash the precipitate by decantation with four 50 cc portions of hot water, passing these washings through the crucible, and finally complete the transfer of the precipitate by means of cold water, dry the crucible and contents at 110 C. for one hour, suspend the crucible within another crucible and ignite gently for forty five minutes adjusting the flame so that the bottom of the lower crucible is heated to dull redness, cool the crucible and contents and weigh the ignited material as bismuth phosphate, use the factor 0.6875 for the conversion of bismuth phosphate to bismuth the amount of bismuth found corresponds to not less than 19.25 per cent nor more than 20.25 per cent

PROPYLENE GLYCOL The propylene glycol used in the preparation of sobisminol mass and sobisminol solution conforms to the New and Non official Remedies standards for this substance, which are

SODIUM BISMUTHATE The sodium bismuthate used in the preparation of sobisminol mass and sobisminol solution conforms to the following tests for identity and purity

Sodium bismuthate occurs as a nearly odorless, yellow brown powder containing not less than 80 per cent of NaBiO_3

Dissolve 1 Gm of sodium bismuthate in a mixture of 5 cc of hydrochloric acid and 15 cc of water a slightly turbid yellow solution results. Agitate 2 Gm of sodium bismuthate with 50 cc of water frequently during one hour the resultant suspension is alkaline to phenolphthalein, filter, rejecting the first few cubic centimeters evaporate 25 cc of the clear filtrate in a tared dish dry the residue at 120 C and weigh the weight of the residue is not more than 0.003 Gm.

Boil 2.5 Gm of sodium bismuthate and 40 cc of water for ten minutes cool dilute to 50 cc with water mix well filter and divide into 10 cc portions to one portion add 0.5 cc of nitric acid and 1 cc of silver nitrate solution the turbidity should not be greater than that produced in a control containing 0.025 mg of chloride ion (chloride), filter, if no residue soluble in a control.

Heat 0.5 fumes of according content sh

Dissolve about 0.25 Gm. of sodium bismuthate accurately weighed in 8 cc of nitric acid dilute with 100 cc of water, and continue the assay for bismuth as directed under sobisminol mass, the amount of bismuth found corresponds to not less than 60.5 per cent nor more than 72.5 per cent.

Transfer about 0.7 Gm of sodium bismuthate, accurately weighed to a flask, allow the excess solution to NaBiO₃ (and standard

TATISOPROPANOLAMINE The trisopropanolamine, $N(C_3H_7OH)_3$ used in the preparation of sobisminol mass and sobisminol solution responds to the following tests for identity and purity

less to pale yellow colored
light characteristic odor and
at a temperature of not less
soluble in acetone, alcohol

The arsenic content of trisopropanolamine is not more than 2 parts per million, heavy metals are absent (U. S. P. XI). Incinerate 5 Gm of trisopropanolamine the weight of the ash does not exceed 0.05 per cent.

Transfer about 5 Gm of trisopropanolamine to a 100 cc volumetric flask and assay for nitrogen as directed under sobisminol mass the

ELI LILLY AND COMPANY

Pulvules Sobisminol Mass• 075 Gm

SOBISMINOL SOLUTION—A solution containing a complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by dissolving the products of the interaction of sodium bismuthate, *friso* propanolamine and propylene glycol in a mixture of propylene glycol and water. Each cubic centimeter of the solution contains between 195 and 205 mg of bismuth and 0.5 cc of propylene glycol.

Actions and Uses—Sobisminol solution is proposed in the treatment of all types of syphilis and is claimed to be free from unusual discomfort when used by the intramuscular injection route. Occasionally lumps in the buttocks follow its intramuscular injection.

Dosage—2 cc intramuscularly into the muscles of the buttocks twice a week. With young children the dosage may be lowered in proportion. Generally a series of from twenty to twenty five injections is considered a course of treatment. In cases of arsenical sensitization the bismuth injections may be continued for a much longer period.

Tests and Standards—

Sobisminol solution occurs as a clear, dark brown red colored liquid, possessing an odor similar to *friso*propanolamine and a sweet mildly metallic taste. It is miscible with an equal volume of water or alcohol.

The pH of a portion of sobisminol solution is not below 11.1 nor above 11.5 as determined by means of a glass electrode. The specific gravity of sobisminol solution is not less than 1.064 nor more than 1.066 at 25°C.

Undiluted sobisminol solution responds to the tests for identity and purity stated under sobisminol mass.

Transfer 5 cc of sobisminol solution accurately measured to a 500 cc beaker and determine the bismuth content according to the method stated under sobisminol mass. The amount of bismuth found is not less than 0.0195 Gm nor more than 0.0205 Gm per cubic centimeter.

Transfer 5 cc of sobisminol solution accurately measured to a 500 cc Kjeldahl flask and determine the nitrogen content according to the method stated under sobisminol mass. The amount of nitrogen found is not less than 0.0054 Gm nor more than 0.0060 Gm per cubic centimeter.

The propylene glycol sodium bismuthate and *friso*propanolamine used in the preparation of sobisminol solution corresponds to the standards for these substances as indicated under sobisminol mass. Sobisminol Solution is manufactured by license of Stanford University under U. S. patent 2,125,561 (Aug. 2, 1938, expires 1955).

ELI LILLY AND COMPANY

Sobisminol Solution 50 cc ampuls

SODIUM IODOBISMUTHITE—Sodium bismuth iodide—A compound formed by the interaction of bismuth chloride and sodium iodide in ethyl acetate solution consisting essentially of hydrated sodium iodobismuthite (sodium bismuth

constant weight is attained the bismuth sulfide weight is equivalent to not more than 21.8 per cent nor less than 20.3 per cent bismuth

Transfer about 0.2 " " " " " " weighed to a 250 cc beaker, " " " " " " to a 250 cc beaker, (prepared by dissolving " " " " " " of water and adding 5 cc of " " " " " " allow to stand two hours filter, using a filter paper, was well with water Without allowing the precipitate to dry, puncture the filter and wash the precipitate into a 250 cc glass stoppered Erlenmeyer flask, using 100 cc of stronger ammonia water agitate the solution, then allow the flask and contents to stand two hours collect the precipitate on a prepared Gooch crucible and wash it with diluted ammonia water then with water, dry to constant weight at 100 C. The weight of silver iodide is equivalent to not less than 60 per cent nor more than 63 per cent iodide Add 10 cc of potassium iodide solution to the filtrate and heat on the steam bath until most of the ammonia has been removed, filter the solution and collect the precipitate on a prepared Gooch crucible wash with water, dry to constant weight at 100 C. the weight of silver iodide is equivalent to not more than 0.7 per cent chloride

SODIUM POTASSIUM BISMUTHYL TARTRATE

—A basic water soluble sodium potassium bismuth tartrate containing from 40.75 to 41.25 per cent of bismuth

Actions and Uses—Sodium potassium bismuthyl tartrate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See preceding article, Bismuth Compounds)

Tests and Standards—

Sodium potassium bismuthyl tartrate is a white heavy powder soluble in water and insoluble in organic solvents

During the ignition of about 0.1 Gm of sodium potassium bismuthyl tartrate in a quartz crucible a small globule of metallic bismuth forms that oxidizes on extended heating The residue is yellow and alkaline to litmus and effervesces with acids

Transfer 0.1 Gm of sodium potassium bismuthyl tartrate to a test tube add 5 cc of water and sufficient diluted hydrochloric acid to dissolve the precipitate first formed and add 0.5 cc of barium chloride solution no cloudiness appears within 2 minutes

Transfer 0.1 Gm of sodium potassium bismuthyl tartrate to a test tube add 5 cc of water and sufficient diluted nitric acid to dissolve the precipitate first formed and add 0.5 cc of silver nitrate solution no precipitate appears

A sample of sodium potassium bismuthyl tartrate loses not more than 0.3 per cent of its weight when dried in a vacuum over sulfuric acid

Transfer about 0.5 Gm of sodium potassium bismuthyl tartrate accurately weighed to an Erlenmeyer flask add 100 cc of water, add diluted hydrochloric acid a drop at a time until the precipitate that forms redissolves saturate with hydrogen sulfide filter wash successively with water alcohol chloroform and ether dry at 100 C. cool in a desiccator and weigh the bismuth sulfide weighed is equivalent to not less than 40.75 per cent nor more than 41.25 per cent of bismuth

THIO-BISMOL—Sodium bismuth thioglycollate—A salt formed by the interaction of sodium thioglycollate and bismuth hydroxide The product has the general formula

$\text{Bi}(\text{SCH}_2\text{CO}_2\text{Na})_3$, though it may differ slightly in composition from this formula. It contains approximately 38 per cent of bismuth

Actions and Uses—Thio-bismol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding general article, Bismuth Compounds); it is a water-soluble compound, readily absorbable, and produces relatively little local injury. A single injection of 0.1 to 0.2 Gm has a definite effect in temporarily stopping the course of a therapeutic malaria.

Dosage—For the average adult, 0.2 Gm administered intramuscularly three times a week for a series of from twelve to fifteen doses.

Tests and Standards—

Thio-bismol occurs as a canary yellow hygroscopic noncrystalline but granular substance possessing a garliclike odor. It is freely soluble in water but the solutions are not stable.

Add 1 drop of diluted hydrochloric acid to 1 cc of a 2 per cent solution of thio-bismol solution; a heavy yellow precipitate separates that dissolves on the addition of another drop of acid. Add several drops of acetic acid to 1 cc of a 2 per cent solution of thio-bismol; no precipitate forms.

Add 1 drop of a 2 per cent solution of thio-bismol to 1 cc of a 2 per cent solution of sodium hydroxide solution, or potassium bisulfite mixture containing about 1 cc of acid to make the solution blackens.

Extract 0.2 Gm of thio-bismol with 10 cc of chloroform or ether; no residue remains after the evaporation of the solvent (free thioglycolic acid). To 1 cc of a 2 per cent solution of thio-bismol add sufficient diluted hydrochloric acid to just dissolve the precipitate first formed and add several drops of barium chloride solution; a precipitate does not appear.

Heat an accurately weighed sample of thio-bismol weighing about 1 Gm in a 100 C oven for one hour; cool in a desiccator and weigh; the sample does not lose more than 5 per cent in weight. Transfer an accurately weighed sample of thio-bismol weighing about 0.4 Gm

PARKE DAVIS & COMPANY

Thio Bismol 02 Gm and 2 Gm ampuls

U S trademark 220 808

Chiniofon

CHINIOFON—*Pulvis Chiniofoni* U S P XI—Chiniofon Powder U S P XI—A mixture of 7 iodo 8-hydroxyquino line 5 sulfonic acid its sodium salt and sodium bicarbonate containing not less than 26.5 and not more than 29 per cent of iodine (I) U S P



For description and standards see the U S Pharmacopeia under Chiniofon and Chiniofon Tablets

Actions and Uses—Chiniofon which is closely similar to preparations introduced under various proprietary names as wound antiseptics has been found to be of use in the treatment of amebic dysentery. It is claimed that the action of the drug is probably due to its absorption and direct action through the blood stream on the amebas invading the bowel wall. The drug has been reported in some cases to produce diarrhea but serious toxic effects do not appear to be common.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endameba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa. Positive diagnosis can often be made by the latter procedure when stool examinations are negative and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases. It is important that negative findings should be checked by stool cultures.

In view of the frequency of persistent infection in the absence of marked symptoms adequate therapy includes reexaminations and repetitions of courses of treatment.

Dosage—Orally for adults from 0.25 to 1.0 Gm in the form of pills, cachets or solutions three times daily for children according to age rectally 1 to 5 Gm freshly dissolved in 200 cc of water at a temperature not exceeding 44 C. The course of treatment requires from seven to fourteen days. Combined oral and rectal administration has been used in acute cases and in the more serious chronic cases accompanied by obstinate clinical symptoms. It has been pointed out that the

iodine content of chiniofon should be considered when chronic endamebiasis is accompanied by thyroid disturbance

Until more evidence becomes available, chiniofon should be used with caution in cases with liver damage

G D SEARLE & CO

Tablets Chiniofon, Enteric Coated: 0.25 Gm The tablets are coated with a mixture of magnesium stearate and shellac

WINTHROP CHEMICAL COMPANY, INC.

Chiniofon (Powder) • bulk

Tablets Chiniofon • 0.25 Gm The tablets are coated with keratin

Mercury Compounds

Mercury has been employed in the treatment of disease since very early in the treatment being used incorporated bases Naturally, when f the early practitioners, it was to be expected that they would employ some of these mercurial ointments for treating the disease Thus mercury inunctions were the first form of mercury employed in treating syphilis Later, Matholi used it internally in the form of red mercuric oxide Still others tried pills of metallic mercury internally, and mercury salts in solutions were also extensively used, for example, van Swieten's sublimate solution In the

intravenous injections of mercury salts have been used only in the past fifty or sixty years One now finds the oral method of administration to be rarely employed It is often the cause of troublesome gastro-intestinal symptoms The inunction method obviates the digestive disturbances If this method is to be

rule, hairy persons do not stand inunctions well, there is a tendency to the development of folliculitis

In more recent years the attempt to improve mercurial therapy has been mainly along two lines the perfection of intramuscular usage and the introduction of the organic compounds

The intramuscular injections are of two types, either of the soluble or of the insoluble salts. As a rule the soluble salts are somewhat more painful and because of their rapid absorption require an injection daily, or at least every other day. They are of great value in getting the patient under rapid mercurialization. For this same purpose one may also employ intravenous injections, though they are not used much in this country. Moreover, these preparations when given intravenously must be given daily if they are to do any good since mercury is so rapidly immobilized, and as a rule daily intravenous injections are scarcely practical. The most popular of the soluble salts are probably mercury bichloride, red mercuric iodide and mercuric succinimide. Mercuric cyanide and mercuric oxycyanide are used considerably in France for intravenous administration.

The claim is made for the insoluble salts of mercury that they do not require administration so frequently and that they are less painful. True, there is danger of a certain amount of cumulative absorption so that it is necessary for the physician to watch the patient very closely when the insoluble salts are being employed. The difference between the mercurous and mercuric compounds is primarily one of solubility and absorption. After the mercurous compounds are absorbed a process that is quite possibly preceded by their oxidation to mercuric compounds, no difference has been demonstrated. Of the insoluble, or perhaps better, semisoluble, salts, mercuric salicylate is probably the best and should be comparatively safe if the patient is observed carefully the injections required being given only once a week. They are quite painful.

In using mercury in the treatment of syphilis the physician should watch the patient carefully for symptoms of intoxication, for example, stomatitis, gastro intestinal symptoms, or symptoms of irritation of the kidneys. Moreover the use of bismuth as an antisyphilitic agent has replaced that of mercury.

Mercuric Compounds

MERCURIC BENZOATE — Hydrargyri Benzoas — Hydrargyrum Benzoicum — $\text{Hg}(\text{C}_6\text{H}_5\text{COO})_2 + \text{H}_2\text{O}$ — The mercuric salt of benzoic acid

Actions and Uses—Mercuric benzoate has been used for intramuscular injections in syphilis and locally in the treatment of gonorrhea but is largely replaced by organic mercury compounds.

Dosage—For intramuscular injection mercuric benzoate is given in a 1 per cent solution by dissolving 0.3 Gm. of mercuric benzoate in 30 cc. of water containing 1.5 Gm. of ammonium

benzoate or given in 2 per cent solution with 2.5 per cent of sodium chloride the average dose being respectively about 0.015 Gm or 0.03 Gm every second day. For urethral irrigation the solution may be 1 in 2000 or 1 in 1000 with an equal quantity of sodium chloride.

Tests and Standards—

Mercuric benzoate is a white crystalline powder slightly soluble in water yielding a weakly acid solution more soluble in an aqueous sodium chloride solution. It is insoluble in alcohol or ether. At 20°C a 10 per cent solution of sodium benzoate dissolves 1 per cent of its weight of mercuric benzoate. With alcohol mercuric benzoate is decomposed into a basic salt having a yellow color.

A solution of 1 Gm of mercuric benzoate and 0.5 Gm of sodium chloride in 20 cc of water yields a black precipitate with hydrogen sulfide and with ferric chloride solution it yields a fawn-colored precipitate of ferric benzoate.

Shake 1 Gm of mercuric benzoate with 20 cc of water and filter. No turbidity is produced when silver nitrate solution is added to 10 cc of the filtrate acidified with a few drops of nitric acid (*chloride*). Two cc of a similar solution when mixed with ferrous sulfate solution to which is added sulfuric acid so as to form a layer beneath should produce no brown coloration at the zone of contact of the two solutions (*nitrates*).

Incinerate about 0.5 Gm of the salt in a porcelain crucible not more than 0.1 per cent of residue remains.

MERCURIC OXYCYANIDE—Hydrargyri Oxycyanidum—Hydrargyrum Oxycyanatum—Mercury Oxycyanide— $\text{Hg}(\text{CN})_2 \cdot \text{HgO}$ —A basic mercuric salt of hydrocyanic acid, containing from 51.7 to 56.0 per cent of mercuric cyanide $[\text{Hg}(\text{CN})_2]$ and from 44.3 to 48.0 per cent of mercuric oxide (HgO).

Actions and Uses—Mercuric oxycyanide has been proposed as a substitute for mercuric chloride. Its antiseptic power is claimed to be greater and it is asserted to be less irritating than mercuric chloride because it does not act on albumin to the same extent. It has advantage over mercuric chloride in that it does not corrode steel instruments.

Representative syphilographers differ as to the use of mercuric oxycyanide intravenously. Some believe that its use should be limited to hospitals, others that it has no advantage over other and safer methods of administering mercury, while others consider it safe and valuable, but all are in accord that its safe use requires experience. It is used quite extensively by the French in the treatment of syphilis generally being employed by the intravenous route.

Dosage—Mercuric oxycyanide may be administered in the same doses as mercuric chloride. It may be applied locally in solutions of 1 in 5000 or somewhat stronger.

MERCURIC SALICYLATE—Contains the equivalent of not less than 54 per cent and not more than 59.5 per cent of Hg^{++} U. S. P.

For description and standards see the U S Pharmacopeia under Mercuric Salicylate and Mercuric Salicylate Injection

Action and Uses—Mercuric salicylate is used by intramuscular injection in the treatment of syphilis

MERCURIC SUCCINIMIDE—When dried over sulfuric acid for 18 hours contains not less than 49.5 per cent and not more than 51 per cent of Hg corresponding to not less than 98 per cent of $C_4H_4N_2O_2Hg$ U S P

For description and standards see the U S Pharmacopeia under Mercuric Succinimide and the National Formulary under Ampuls of Mercuric Succinimide

Actions and Uses—Mercuric succinimide has the action of other salts of mercury but its solutions are said to be relatively nonirritating. The preparation is used as are other compounds of mercury in the treatment of syphilis

Dosage—Mercuric succinimide is used mainly by intramuscular injection. The daily dose is from 10 mg to 20 mg given in the form of a 2.5 per cent solution (from 0.5 to 1 cc of such solution). Mercuric succinimide may be given by the mouth in doses of from 10 mg to 15 mg

SOLUTION COLLOIDAL MERCURY SULFIDE HILLE—Liquor Hydrargyri Sulfidis Colloidalis—Solution Colloidal Mercuric Sulfide Solution Mersulfol—A colloidal 2 per cent solution of mercuric sulfide in water, stabilized with a hydrolyzed protein substance and preserved with 0.2 per cent of tricresol

Actions and Uses—Solution colloidal mercury sulfide Hille is proposed for intramuscular injection in the treatment of syphilis

Dosage—The usual dose is from 2 to 3 cc administered intramuscularly twice a week for a course of sixteen to twenty injections. With intermittent treatment there should then be a rest period of six or eight weeks. If continuous therapy is being used of course some other antisyphilitic for example arsphenamine might then be employed

Tests and Standards—

Solution colloidal mercury sulfide Hille is black in reflected light and brown in transmitted light. It possesses the odor and taste of cresol. It has a specific gravity of from 1.0670 to 1.0690

Solution colloidal mercury sulfide Hille is neutral to litmus. (Place a drop of the solution over a piece of blue litmus paper and a drop of the solution add a few drops of 10% sodium hydroxide solution which will give a red precipitate. Add 7 Gm of 10% sodium hydroxide solution to the precipitate and the precipitate will remain clear.)

(lead), dilute the filtrate to 25 cc. Transfer about one fourth of the black precipitate to a beaker, add 10 cc of water, 2 cc of diluted hydrochloric acid and a small crystal of potassium chlorate boil until the solution no longer evolves chlorine, filter off the sulfur and add a few drops of stannous chloride a white precipitate that changes to gray forms. To 5 cc of the yellowish filtrate add 5 cc of ammonia water no color change occurs (*copper*) and no precipitate forms (*bismuth iron*). To 5 cc of the filtrate, add 1 cc of a 1 per cent solution of tannic acid a white precipitate forms. To 5 cc of the filtrate add 2 drops of a 36 per cent solution of acetic acid a turbidity appears that disappears on the addition of more acetic acid. To 5 cc of the filtrate add 1 cc of copper sulfate solution a slight precipitate forms that is rendered soluble by adding 2 volumes of water add 1 cc of normal sodium hydroxide solution a violet color appears. To 5 cc of the filtrate add 1 cc of mercuric chloride solution no precipitate forms. To 5 cc of the original solution add 5 cc of diluted hydrochloric acid and a small crystal of potassium chlorate and heat. When the black precipitate has disappeared filter and boil to a small volume. Add 2 cc of sulfurous acid and continue the boiling until sulfur dioxide is no longer given off, cool this solution conforms to the U S P test for arsenic.

Transfer exactly 3 cc of solution colloidal mercuric sulfide Hille to a weighed platinum dish add sodium sulfide solution (50 Gm sodium sulfide dissolved to make 100 cc) until the precipitate just dissolves and then add as much again electrolyze the solution for six hours using 6 volts wash with water, alcohol and ether, dry in a desiccator containing sulfuric acid and a beaker containing metallic mercury weigh the mercury calculated to mercuric sulfide is not less than 1.94 per cent nor more than 2.06 per cent.

HILLE LABORATORIES

Solution Colloidal Mercury Sulfide. 30 cc and 60 cc rubber-stoppered vials

Iodine Compounds

DIODOQUIN—57 Diodo 8 hydroxyquinoline, $C_8H_6N_2O$. I₂.—A compound resulting from the introduction of two atoms of iodine into 8 hydroxyquinoline



Actions and Uses—Diodoquin is proposed as an antiprotozoan agent for use in amebic dysentery and in the treatment of *Trichomonas hominis* (intestinalis) infections.

Dosage—Adults—seven to ten tablets a day for fifteen to twenty days.

Tests and Standards—

Diodoquin occurs as a yellowish brown practically odorless powder. It is almost insoluble in water, sparingly soluble in alcohol, ether and acetone, soluble in hot pyridine and in hot dioxane. Diodoquin melts between 200 and 215 C with extensive decomposition.

Warm a few crystals of diodoquin with 1 cc of concentrated sulfuric acid vapors of iodine are evolved. Heat 0.5 Gm of diodoquin mixed with 5 Gm of anhydrous sodium carbonate in a deep crucible cool, extract the mixture in 10 cc of water, acidify with diluted nitric acid. Filter and add 13 cc of tenth normal silver nitrate solution to the filtrate. Shake to coagulate the precipitate and filter. Add 1 cc of tenth normal silver nitrate solution to the filtrate, shake and filter through a fresh filter paper. Wash the precipitate on the filter. A yellow color is observed (*distinction from iodoform which gives a white precipitate*).

Dry 1 Gm of diodoquin over phosphorus pentoxide for twenty-four hours. The loss in weight is less than 0.1 per cent.

Incinerate about 1 Gm of diodoquin. The ash is not over 0.5 per cent.

Mix about 0.15 Gm of diodoquin, accurately weighed in a nickel crucible with 5 Gm of anhydrous potassium carbonate (or sodium carbonate). Mix thoroughly with a dry stirring rod, settle the mixture by tapping the crucible overlay with 5 Gm of potassium carbonate (or sodium carbonate) and ignite at about 600 C. for from three to five minutes. Cool, transfer the crucible to a 500 cc wide mouth conical flask and extract with about 20 cc of distilled water. Acidify the solution carefully, dropwise with five normal hydrochloric acid (about 30 cc). Filter the solution quantitatively into a 250 cc glass stoppered flask using two 20 cc portions of water to rinse the flask and filter paper. The volume at this point should be about 100 cc. Add a cooled mixture of 35 cc of hydrochloric acid 35 cc of distilled water and add 10 cc of purified chloroform. Titrate with tenth normal potassium iodate to the disappearance of pink color in the chloroform layer (add iodate solution dropwise and shake vigorously near the endpoint). One cc. of tenth normal potassium iodate solution is equivalent to 0.00123 Gm of iodine. Diodoquin contains not less than 60.5 per cent nor more than 64.0 per cent of iodine.

G. D. SEARLE & Co

Tablets Diodoquin: 0.21 Gm

U. S. trademark 336 484

Quinine Derivatives

The action of quinine is essentially the same in all its compounds. The official salts have the disadvantage of the bitter taste, and of producing a local action on the stomach and other tissues. To obviate these difficulties, insoluble compounds like the alkaloid or the tannate have been used, since these pass the mouth and stomach without offending the taste or disturbing the stomach. The same object is obtained more or less completely in a number of radical is combined bionic acid, to form

or less rapidly its. The rapid-determine to a effect and the

large extent liability to produce cinchonism. Where oral medication is not feasible quinine derivatives may be administered by intravenous injection, but this should be reserved for emergency cases of marked fall in blood pressure. The salts should be diluted to a

concentration not greater than 0.5 per cent and should be injected very slowly. The subcutaneous or intramuscular routes should not be employed because of the danger of local tissue damage. In those rare cases where neither oral nor intravenous administration is possible, the use of other antimalarial drugs should be resorted to.

Some of the esters also contain other therapeutically active radicals (phenetidin salicyl, etc.) When liberated these produce their characteristic effects, but it is doubtful whether the combinations of several therapeutically active radicals in fixed proportions are superior to simple mixtures of the ingredients.

Totaquine, U. S. P., which is a mixture of alkaloids from the bark of species of *Cinchona* containing not less than 70 per cent of the total crystallizable alkaloids has been developed for use in the treatment of malaria in the same manner as quinine compounds.

QUININE DIHYDROCHLORIDE — The dihydrochloride of an alkaloid obtained from cinchona "U. S. P."

For description and standards see the U. S. Pharmacopeia under Quinine Dihydrochloride and the National Formulary under Ampuls of Quinine Dihydrochloride.

Actions and Uses — Quinine Dihydrochloride has actions similar to those of quinine, over which it has the advantage of being more soluble in water. It is used where aqueous solutions of quinine are desired for intravenous injection in those cases of severe malarial infection where oral medication is not feasible. It should not be administered by subcutaneous or intramuscular injection because of the danger of local tissue damage. The absorption of intramuscular injections of quinine salts is slower than that following oral administration. Solutions of quinine dihydrochloride for intravenous administration should be diluted to a concentration not greater than 0.5 per cent and should be given slowly and with due cognizance of the danger of a serious fall in blood pressure particularly in patients with cardiovascular impairment.

Dosage — From 0.24 to 0.65 Gm. suitably diluted, is given intravenously as indicated by the severity of the symptoms and the age of the patient. The dose of 0.65 Gm. should not be repeated more than three times in twenty-four hours. Oral administration should be resumed as early as possible.

ENDO PRODUCTS, INC.

Solution Quinine Dihydrochloride 0.25 Gm. in 1 cc., 0.5 Gm. in 1 cc., 1.0 Gm. in 2 cc. ampuls. Each ampul contains the stated amount of quinine dihydrochloride dissolved in distilled water.

QUININE DIHYDROCHLORIDE AND URETHANE—A sterile aqueous solution containing quinine dihydrochloride U S P 127 Gm and ethyl carbamate U S P 66 Gm. in each hundred cubic centimeters

For standards see U S Pharmacopœia under Quinine Dihydrochloride and Ethyl Carbamate

Actions and Uses—A mixture of quinine dihydrochloride and urethane in aqueous solution is used as a sclerosing agent for injection in the obliterative treatment of varicose veins. The mixture is claimed to have antiseptic qualities. It should not be used in the presence of any infection or in the presence of deep veins.

Dosage—The initial injection should be limited to 0.5 cc. to determine whether idiosyncrasy exists. Average amount for injection at any one site is 1 cc. and should not exceed 2 cc. The total quantity to be injected at a single sitting should not exceed 5 cc. to avoid the production of cinchonism. The injection should be made slowly to avoid dangerous consequences.

QUININE ETHYLCARBONATE—Euquinine—The ethylcarbonate of an alkaloid obtained from cinchona." U S P

For description and standards see the U S Pharmacopœia under Quinine Ethylcarbonate

Actions and Uses—Quinine ethylcarbonate is used in place of quinine sulfate and similar soluble quinine salts when a practically tasteless quinine compound is preferred.

Dosage—1 Gm.

MALLINCKRODT CHEMICAL WORKS

Quinine Ethyl Carbonate (*Powder*) bulk.

MERCK & CO. INC.

Quinine Ethyl Carbonate (*Powder*) bulk.

QUININE SULFATE—"The sulfate of an alkaloid obtained from cinchona." U S P

For description and standards see the U S Pharmacopœia under Quinine Sulfate

ELI LILLY AND COMPANY

Coco Quinine Each 100 cc. contains quinine sulfate 2.19 Gm. suspended in a syrup flavored with chocolate, yerba santa and vanilla and containing sodium benzoate 0.18 Gm. per 100 cc., and alcohol 4 per cent.

U S trademark 174 144

Anthelmintic Agents

CARBON TETRACHLORIDE—U S P Tetrachlor methane

For description and standards see the U S Pharmacopeia under Carbon Tetrachloride and Carbon Tetrachloride Capsules

Actions and Uses—Carbon tetrachloride has narcotic and anesthetic properties somewhat similar to those of chloroform. It has recently come into use as a vermifuge in the treatment of hookworm disease. It is reported that usually about 95 per cent of the hookworms are removed by the first dose of carbon tetrachloride and that occasionally all are removed. As a vermifuge it appears to be relatively safe but serious symptoms and even death have occurred especially in patients addicted to the use of alcohol. During treatment some of the patients complain of headache. Good results are obtained by administration in water or milk or in gelatin capsules on an empty stomach followed in three hours by a purgative dose of magnesium sulfate. The capsules may be prepared extemporaneously. Lambert recommends giving the vermicide and a solution of magnesium sulfate together claiming that this prevents headache. A mild laxative is generally given to constipated patients on the day preceding treatment. To be a complete remedy of the hook-

ment

Dosage—From 2 to 3 cc. For children 0.13 cc. for each year of age up to 15 years. The capsules should be swallowed immediately not broken in the mouth. A purgative dose is administered two or three hours after the anthelmintic. A laxative dose of the salt should be administered also on the preceding day. The dose of 3 cc. should not be exceeded.

MEYER & CO. INC.

Carbon Tetrachloride (*Liquid*) bulk

— Perchloroethylene —
at least 99 per cent
the remainder consist

For description and standards see the U S Pharmacopeia under Tetrachloroethylene and Tetrachloroethylene Capsules

Actions and Uses—Observations of many workers have shown that tetrachloroethylene is a useful anthelmintic for the treatment of hookworm infestation. It has been used against other worms with less success although there is some evidence that it is useful in *Trichuris* infestation. It may be lethal to

Ascaris but its use in that infestation is not advised because of the danger of causing migration of the worms. It is the consensus of the investigators that tetrachlorethylene is less toxic than carbon tetrachloride (CCl_4) and at least as efficacious as the latter drug. It has a further advantage over carbon tetrachloride in that it does not raise the guanidine content of the blood which is important in cases exhibiting a calcium deficiency. Untoward reactions are rare but giddiness vomiting and drowsiness have been reported in some cases. It is probably better to keep the patient (especially children) in bed during the treatment.

Dosage—From 1 to 3 cc depending on the age of the patient. Tetrachlorethylene is usually given in soft gelatin capsules but has also been administered to children on a lump of sugar. The gastro intestinal tract should be thoroughly washed with water. Fats and alcohol should be avoided. Absorption of the drug is followed by a saline cathartic. One dose frequently repeated once after a period

of from ten days to two weeks.

NOTE—Broken capsules should be discarded. The solution should never be employed if it has been exposed to the air for more than a very brief time because of the possibility of phosgene formation by decomposition.

CHAPTER VI

ANTISPASMODIC PREPARATIONS

INTOCOSTRIN—A curare preparation containing therapeutically desirable constituents of curare

Actions and Uses—Intocostrin has been shown by physiologic tests to have a substantially pure curare action, that is it paralyzes the skeletal muscles. This paralysis results from an interruption of the nerve impulse at the myoneural junction. The diaphragm and intercostal muscles are usually the last to be affected. The action of the drug is brief because of rapid excretion and destruction. If respiration is embarrassed or arrested neostigmine, a physiologic antidote will assist in counteracting the curare effect but properly instituted artificial respiration may be necessary to maintain respiration until the activity in intoxication is alkaloid d. tubo total solids in into and chlorobutanol

This alkaloid has been isolated as a pure crystalline salt. Intocostrin may be used to soften the severity of convulsions and to prevent fractures in shock therapy of mental diseases, to produce muscular relaxation during the reduction of fractures or dislocations or during certain manipulative diagnostic procedures to produce a more or less transient reduction of hypertonia, tremor, incoordination, athetosis and dysarthria in certain neurologic conditions and with certain precautions to aid in the diagnosis of myasthenia gravis.

Intocostrin can be used by those experienced in such use as an adjuvant to anesthesia. The drug is not however, without its dangers. Overdosage produces paralysis of the respiratory

value of Intocostrin in anesthesia is the development of adequate muscular relaxation. It is claimed that the amount of anesthetic and depth of anesthesia may be decreased.

Dosage—In softening the convulsions of shock therapy or to produce relaxation in manipulative procedures 0.5 unit per pound of body weight (but the initial dose for adults should be 20 units less than this total), administered intravenously at a uniform rate during one to one and one half minutes. Larger doses may be necessary but if the estimated dose fails to produce paralysis another for twenty-four hours cope with respiratory should be at hand.

airflow should be available on the tray to assist in artificial respiration in the event of obstructed breathing. In spastic and athetoid states in children 0.5 to 1.5 units per pound of body weight administered intramuscularly at four day intervals. As a diagnostic agent in myasthenia gravis one fifteenth to one fifth of the average adult dose intravenously followed always in two or three minutes by the intravenous injection of 15 mg. of neostigmine methylsulfate with 0.65 mg. of atropine sulfate.

In order to obtain muscular relaxation during light (second plane) anesthesia with cyclopropane nitrous oxide or barbiturates 40 to 60 units of intocostrin may be administered when the skin incision is made. 20 to 30 units may be added in three to five minutes if needed. If the operation has lasted more than forty five minutes an additional dose of 30 to 40 units may be cautiously administered if such additional dosage seems indicated. In an alternative method as much as 100 units has been administered at the beginning of the operation. Small quantities should be administered at intervals of time as time has elapsed.

and then extreme caution exercised. The drug apparently may be used with any type of anesthetic agent although with ether only about one third of the dose otherwise employed should be used. It must be remembered however that the use of intocostrin as an adjuvant to surgical anesthesia is still in a stage which requires continued careful study.

Curare has been extensively used with sodium pentothal anesthesia usually by separate injection. If a barbiturate solution (alkaline) is mixed with a curare solution (acid) a precipitate is formed which is of the nature of a curare-barbiturate complex. The barbiturate with its free barbiturate is in solution. The curare is alkalized with sodium carbonate no loss in potency occurs during a twenty four hour period and no precipitate forms when the alkalized solution is mixed in any quantity with a barbiturate solution. Such mixtures have not been used clinically the present method is to inject the solution separately and alternately through a Y tube using the same needle. When by this method intocostrin follows the barbiturate a slight fine precipitate forms at the surface of contact of the two solutions. It has been the custom to allow such a precipitate to be injected slowly as it presumably redissolves on mixing with the plasma.

Preparation—

Intocostrin prepared from *Chondodendron tomentosum* extract is made by first extracting with alcohol a desiccated curare obtained from a heavy syrup of the bark and stems of *Chondodendron tomentosum*. The alcoholic extract is evaporated to dryness a sterile filtered solution having a pH of 4.648 is made and adjusted to a standard potency of 20 units per cubic centimeter. The final solution contains sodium chloride 0.45 per cent and trichlorobutanol 0.5 per cent sterilized by filtration and its pH again adjusted to 4.648.

Tests and Standards—

Dilute in a large pyrex test tube 0.25 cc of intocostin with 25 cc of distilled water and add 0.2 cc of concentrated sulfuric acid and 2 cc of 1 per cent potassium iodate solution. Mix and warm in a water bath at 50 C for one half hour. A yellow color is developed.

The physiologic activity of intocostin is determined on rabbits. The provisional unit is equivalent to the potency of 0.15 mg of diubocurarine chloride.

E. R. Squinn & Sons

Intocostin Solution: 5 cc and 10 cc vials. Each cubic centimeter contains an amount of intocostin equivalent to 20 units sodium chloride 0.45 per cent and chlorobutanol 0.5 per cent as a preservative.

CHAPTER VII

ASTRINGENTS AND CAUSTICS

Aluminum Salts

Several of the compounds of aluminum are official, including the ordinary alum or alumen, U S P. Aluminum acetate and aluminum subacetate are used in the form of solutions and are described in the National Formulary as Solution of Aluminum Acetate and Solution of Aluminum Subacetate.

The aluminum compounds are used for their astringent action. Since they are but little absorbed, they are relatively nontoxic.

Compounds of aluminum are astringent because of their property of precipitating albumin. The exsiccated alum is more energetic, not only because it contains a larger proportion of alum than the crystalline form but because it absorbs water from the tissue at the same time. The acetate is milder than the sulfate, as is usual with metallic salts.

The aluminum compounds are not so astringent as the corresponding lead salts, but they may exert an irritant and even caustic action when used in concentrated solutions or in the form of the exsiccated (burnt) alum. When swallowed in over doses in such concentrated form, they may cause gastritis and diarrhea. Alum is sometimes used as an emetic.

The aluminum compounds are slightly antiseptic, a property which goes with their astringency. Some of the organic compounds are said to be more actively antiseptic than the inorganic ones.

Several proprietary preparations, consisting of aluminum combined with organic acids, have been introduced with a view to utilizing the astringent and antiseptic properties of their components. Many of these possess no special advantages and have fallen into disuse, or have been largely replaced by others of a more or less similar nature.

Aluminum compounds in the form of gels used as antacids are described in the chapter on Gastrointestinal Drugs.

Copper Salts

COPPER CITRATE—*Cupri Citras*—*Cupric Citrate*—The cupric salt of citric acid, containing from 34 to 36 per cent of copper.

Actions, Uses and Dosage—Copper citrate possesses the astringent and antiseptic properties of other salts of copper somewhat modified by its sparing solubility.

It may be used for the same purposes as and in doses similar to those of other salts of copper.

Tests and Standards—

Copper citrate occurs as a green or bluish green finely crystalline odorless powder. It is slightly soluble in cold water, somewhat more soluble in a cold solution of an alkali citrate, forming a greenish blue solution, more soluble in a hot solution of an alkali citrate, also soluble with decomposition in ammonia water and in mineral salts.

When dissolved in ammonia water, copper citrate yields an intense blue solution. When heated to 90 C., the salt loses water of hydration and assumes a pale blue color. At a higher temperature it blackens and at a low red heat leaves a black residue of cupric oxide. If about 1 Gm. of copper citrate is dissolved in 20 cc. of diluted hydrochloric acid, the solution diluted to 200 cc. with hot water, the mixture saturated with hydrogen sulfide, filtered, and the filtrate evaporated nearly to dryness on the water bath, the residue responds to the usual tests for citric acid. If 0.5 Gm. of copper citrate is dissolved in 10 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution added, no immediate turbidity occurs. A solution of 0.5 Gm. of the salt in 10 cc. of diluted sulfuric acid should not evolve any odor of acetic acid when boiled. The salt should be free from nitrates, chlorides and carbonates.

To about 0.5 Gm. accurately weighed, add 25 cc. water and 10 cc. of normal sulfuric acid. Heat the mixture almost to boiling until solution is complete, adding a little more acid if necessary. Cool the solution and add 10 cc. of potassium iodide solution and allow it to stand five minutes with occasional shaking. Add 200 cc. of water and titrate the liberated iodine with tenth normal sodium thiosulfate; the titration should indicate not less than 91 per cent of copper.

MALLINKRODT CHEMICAL WORKS

Copper Citrate (Crystals)• bulk

MANHATTAN EYE SALVE COMPANY, INC.

Ophthalmic Ointment Copper Citrate 5 per Cent. A sterile ointment containing copper citrate 5 per cent, wool fat 10 per cent, petrolatum 85 per cent, without alcohol or preservative.

Ophthalmic Ointment Copper Citrate 10 per Cent. A sterile ointment containing copper citrate 10 per cent, wool fat 10 per cent, petrolatum 80 per cent, without alcohol or preservative.

Pyrogallol

LENIGALLOL — Pyrogallolis Triacetate — Triacetyl pyrogallol $C_6H_3(CH_3CO_2)_3$ —Pyrogallol triacetate, obtained by replacing the hydroxyl groups of pyrogallol with acetate groups.

It is a white, crystalline solid, melting at 100° C. It is soluble in alcohol, ether, and chloroform. It is used as a local anesthetic and in the treatment of skin diseases.

acute and subacute eczema of children and other skin diseases.

Dosage—In 5 to 10 per cent ointment, usually with zinc oxide.

Tests and Standards—

Lenigallol is prepared by boiling 10 parts of pyrogallol, 1 part sodium acetate and 25 parts of acetic anhydride for two hours and washing the crystalline product on a filter with water.

It is a white, crystalline powder, melting at 165 C. It is insoluble in water, but soluble with decomposition in warm aqueous alkalis.

Lenigallol is incompatible with alkalis, strong acids and oxidizing agents.

BILHUBER-KNOIL CORP.

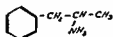
Lenigallol-Zinc Ointment: Contains lenigallol 6 per cent, in zinc oxide ointment-U. S. P.

CHAPTER VIII

AUTONOMIC DRUGS

Sympathomimetic Agents

AMPHETAMINE—Racemic Amphetamine—Alpha-methylphenethylamine—1-phenyl 2-aminopropane—Benzedrine—Racemic desoxy nor ephedrine—A synthetically prepared racemic mixture of bases having the formula $C_6H_5CH_2CH(NH_2)CH_3$.



Actions and Uses—Amphetamine produces local effects similar

use in therapeutic doses

as a result of overdosage and what may be hypersensitivity to the drug in inhalator form

Tests and Standards—

Amphetamine occurs as a colorless mobile liquid, boiling at 200 203 C., with slight decomposition. The specific gravity at 25 C. is 0.931. The vapor pressure at ordinary temperature is relatively high, and the substance possesses a strong basic odor and a burning

Suspend about 1 Gm. of amphetamine, accurately weighed, in 10 cc. of water and titrate with half-normal sulfuric acid, using methyl red as an indicator; the acid used corresponds to not less than 95 per cent nor more than 100 per cent of the base (1 cc. half-normal sulfuric acid is equivalent to 0.0675 Gm. of base).

Determine carbon hydrogen and nitrogen by micro combustion methods. The carbon should be not less than 79.7 nor more than 80.2 per cent, the hydrogen not less than 9.6 nor more than 9.9 per cent, and the nitrogen, not less than 10.2 nor more than 10.6 per cent.

AMPHETAMINE SOLUTION Transfer an accurately weighed sample of benzedrine solution weighing about 15 Gm in a Kjeldahl distillation flask, add 5 Gm of tale, 250 cc of water and 1 Gm of sodium hydroxide, distil 150 cc into 20 cc of tenth normal sulfuric acid, titrate the excess acid with tenth normal sodium hydroxide solution the base is equivalent to not less than 0.95 per cent nor more than 1.05 per cent.

Transfer the foregoing solution to a separatory funnel and proceed to determine the melting point of benzoyl derivative as outlined under "Benzedrine Inhaler."

SMITH, KLINE & FRENCH LABORATORIES

Benzedrine Inhaler: Each inhaler tube contains, at the time of packing, amphetamine 0.20 Gm, menthol 10 mg and aromatics.

U S patents 1921424 (Aug. 8, 1933, expires 1950) and 1879,003 (Sept. 27, 1932, expires 1949) U S trademarks 272,377 and 330,017

BENZEDRINE INHALER Transfer the filling to a Kjeldahl distillation flask add 250 cc of water and 1 Gm. of sodium hydroxide, distil 150 cc into 20 cc of tenth normal sulfuric acid, titrate the excess acid with tenth normal sodium hydroxide solution the base is equivalent to not less than 0.200 Gm nor more than 0.230 Gm. per tube.

Transfer the solution from titration to a separatory funnel extract with 30 cc of ether transfer the aqueous layer to an Erlenmeyer flask add 2 cc of 40 per cent sodium hydroxide solution and 0.5 cc of benzoyl chloride and shake the flask and contents for ten minutes set aside for two hours, add 0.5 cc of benzoyl chloride, shake the flask and contents for ten minutes set aside, at the end of two hours add 0.5 cc. of benzoyl chloride shake the flask for ten minutes allow to stand on the steam bath until the odor of benzoyl chloride has disappeared remove the precipitate by filtration, wash with cold water dry at 90 C, the melting point is 130-135 C.

AMPHETAMINE SULFATE

Sulfate—

fate—Ra

propane

Actions and Uses—Amphetamine sulfate has a number of clinical uses. It has been widely employed in the treatment of narcolepsy, in controlling the oculogyric crises and various other manifestations of postencephalic parkinsonism as an adjunct in the treatment of alcoholism, and for facilitating roentgenographic studies of the gastrointestinal tract, but its most extensive therapeutic application has been in the treatment of certain depressive conditions especially those characterized by apathy and psychomotor retardation.

The marked central nervous stimulatory effect of the drug on the central nervous system renders it effective in the symptomatic treatment of many mild psychogenic depressive states such as those associated with prolonged convalescence bereavement or misfortune the postpartum period the menopause old age etc.

Amphetamine sulfate may also be of value but to a lesser extent, in the symptomatic treatment of the more severe depressions accompanying certain major psychopathic conditions.

There is considerable evidence that, again due to its amelio-

more fundamental psychotherapeutic measures. In acute alcoholism, with or without accompanying psychosis the drug may occasionally be useful in combating pathologic intoxication (In alcoholic psychoses best results are reported where the psychosis is of recent origin.)

In addition, the drug has been reported to be effective in the symptomatic treatment of orthostatic hypotension. It has also been used in spastic colitis, pyloric spasm, and certain other clinical conditions not mentioned above, but such use is not recommended.

Mixtures (not accepted by the Council for New and Non-official Remedies) containing amphetamine sulfate have been exploited for use in obtaining weight reduction. The Council has considered the evidence for such claims and has reached the conclusion that whatever effectiveness the drug might have might possibly be due to undesirable properties. The Council therefore, has gone on record as disapproving general recognition of claims for the use of amphetamine sulfate in the treatment of obesity.

While the drug is useful in the treatment of various depressive states, evidence indicates that it is of little value in altering the course of the underlying psychosis in the major psychopathic conditions. Obviously, in severe depressive psychopathic

occurred when the drug has been so used. Except when administered under the strict supervision of the physician, its use is not recommended for developing a sense of exhilaration, increased energy and capacity for work, nor as a "pick me up" following temporary alcoholic overindulgence.

Because of the inherent pharmacological nature of amphetamine, the physician should be fully aware of the possibility that its administration may, in certain instances, produce overstimulation, restlessness, sleeplessness, and gastrointestinal disturbance, and that overdosage may be followed by chills, collapse and syncope.

the drug although cases of habit formation have only rarely been reported must be kept in mind

Dosage—Since effective dosage varies considerably with the individual patient and with the condition being treated initial doses should be small (5 mg, or less) and should be increased gradually until a definite effect manifests itself. The use of a small test dose is particularly important in the treatment of depressive states. In most cases it is desirable to administer the drug in divided doses. To avoid interference with sleep the final daily dose should ordinarily not be given later than 4 p. m. The usual therapeutic dosage range is from 5 to 30 mg though larger doses are occasionally given.

Tests and Standards—

Amphetamine sulfate occurs as a white odorless powder, freely soluble in water, slightly soluble in alcohol, insoluble in ether. A solution of 1 Gm. in 10 cc. of water has a *pH* between 5.0 and 6.0. Amphetamine sulfate melts at over 300° C. with decomposition.

Place 1 Gm. of amphetamine sulfate in an Erlenmeyer flask, add 50 cc. of water and 5 cc. of 40 per cent sodium hydroxide solution, then add benzoyl chloride 0.5 cc. at a time, shake the flask after each addition, add the benzoyl chloride until no more precipitate forms, after an addition recrystallize twice from 50 per cent alcohol solution, dry the crystals, the melting point is 134–135° C., the nitrogen content of the benzoyl derivative by the micro Dumas method is not less than 5.70 per cent nor more than 5.95 per cent.

Dry about 0.5 Gm. of amphetamine sulfate accurately weighed to constant weight at 100° C., the loss does not exceed 1 per cent. Incinerate about 0.5 Gm. of amphetamine sulfate accurately weighed, the residue is not more than 0.1 per cent.

Transfer 0.3 Gm. of amphetamine sulfate accurately weighed to a beaker and dissolve in 200 cc. of water and 2 cc. of normal hydrochloric acid. Boil and add 10 cc. of boiling 10 per cent barium chloride solution. Allow to stand overnight, filter, wash until free from chloride, ignite at low red heat to constant weight, cool and weigh, the sulfate content is not less than 25.5 per cent nor more than 26.4 per cent.

Dissolve 0.25 Gm. of amphetamine sulfate accurately weighed in 25 cc. of water in a separatory funnel. Add 3 cc. of 10 per cent sodium hydroxide solution and extract with six 15 cc. portions of

SMITH, KLINE & FRENCH LABORATORIES

Benzedrine Sulfate Powder

Benzedrine Sulfate Elixir 177 cc. bottles. Each 5 cc. contains racemic amphetamine sulfate 25 mg. and alcohol 10 per cent.

sidered safe. Ephedrine is used to sustain the blood pressure in spinal anesthesia but it is still questionable whether the drug is of real benefit in shock, hypotension and circulatory collapse and hemorrhage. It is of value in preventing the muscle weakness of myasthenia gravis. It is without value in Addison's disease.

Dosage—Salts of ephedrine are quite effective whether given orally, intramuscularly, intravenously, or by any ordinary path of administration. For local application to mucous membranes it is used in 0.5 to 2 per cent solution of a salt of ephedrine, in ophthalmologic work it has been used in 4 per cent solution. Orally the usual dose for adults is from 20 to 50 mg. every 3 to 4 hours.

ABBOTT LABORATORIES

Ephedrine (Powder) bulk

GANE AND INGRAM, INC

Ephedrine (Powder) bulk

MERCK & CO, INC

Ephedrine (Powder) bulk

EPHEDRINE HYDROCHLORIDE—When dried over sulfuric acid for 18 hours contains not less than 80 per cent and not more than 82.5 per cent of anhydrous ephedrine ($C_{10}H_{15}NO$) U S P

For description and standards see the U S Pharmacopoeia under Ephedrine Hydrochloride and the National Formulary under Tablets of Ephedrine Hydrochloride.

Actions and Uses—See preceding article Ephedrine.

Dosage—See preceding article Ephedrine.

ABBOTT LABORATORIES

Solution Ephedrine Hydrochloride 5 per Cent 1 cc ampuls

Solution Ephedrine Hydrochloride 3 per Cent Preserved with chlorobutanol, 0.5 per cent

Syrup Ephedrine Hydrochloride Contains ephedrine hydrochloride 0.2195 Gm. in 100 cc. and alcohol 12 per cent

Syrup Ephedrine Hydrochloride (Double Strength) Containing ephedrine hydrochloride 0.4390 Gm. in 100 cc. and alcohol 12 per cent

Tablets Ephedrine Hydrochloride 32.5 mg

Ephedrine Hydrochloride 2½%, and Procaine Hydrochloride 1%, Solution 2 cc ampule

Ephedrine Hydrochloride 5%, and Procaine Hydrochloride 1%, Solution 2 cc ampule

U. S. patent 1,260,289 (March 26 1918 exp. red)

AMERICAN PHARMACEUTICAL CO., INC

Solution Ephedrine Hydrochloride, 3 per Cent 1 fluid ounce bottle Preserved with 0.5 per cent chlorobutanol

Capsules Ephedrine Hydrochloride 25 mg and 50 mg

GEORGE A BREON & COMPANY, INC

Caplets Ephedrine Hydrochloride 50 mg

Solution Ephedrine Hydrochloride 3%, 29.5 cc. and 480 cc bottles 0.5 per cent chlorobutanol added as preservative

BURROUGHS WELLCOME & Co., INC

Ephedrine Hydrochloride (Powder) 15 cc. and 30 cc bottles

Ephedrine Hydrochloride Injection 30 mg in 1 cc hypodermic

Solution Ephedrine Hydrochloride 3 per cent Preserved with chlorobutanol 0.5 per cent 1 fluidounce and 1 pint bottles

Tabloid Ephedrine Hydrochloride 16 mg and 32 mg

ENDO PRODUCTS INC

Capsules Ephedrine Hydrochloride 24 mg 324 mg and 49 mg

GANE AND INGRAM, INC

Ephedrine Hydrochloride (Powder) bulk

ELI LILLY AND COMPANY

Pulvules Ephedrine Hydrochloride 25 mg and 50 mg

Solution Ephedrine Hydrochloride, 3 per cent Preserved with chlorobutanol 0.5 per cent

Solution Ephedrine Hydrochloride 25 mg per cc 1 cc ampule

Syrup Ephedrine Hydrochloride Contains ephedrine hydrochloride 0.22 Gm in 100 cc and alcohol 12 per cent it is flavored with varillin benzaldehyde and tolu and tinted with amaranth

MERCK & Co, INC

Ephedrine Hydrochloride (Powder) bulk

PARKE, DAVIS & COMPANY

Capsules Ephedrine Hydrochloride 25 mg and 50 mg

PITMAN MOORE COMPANY

Capsules Ephedrine Hydrochloride 24 mg

SHARP & DOHME INC

Capsules Ephedrine Hydrochloride 25 mg

WARREN TEED PRODUCTS COMPANY

Capsules Ephedrine Hydrochloride 25 mg and 50 mg

EPHEDRINE SULFATE—When dried over sulfuric acid for 18 hours contains not less than 75.5 per cent and not more than 77.3 per cent of anhydrous ephedrine ($C_{10}H_{15}NO$)
U S P

For description and standards see the U S Pharmacopeia under Ephedrine Sulfate and Ephedrine Sulfate Tablets and the National Formulary under Ampuls of Ephedrine Sulfate Jelly of Ephedrine Sulfate Solution Ephedrine Sulfate and Syrup of Ephedrine Sulfate

Actions and Uses—See preceding article Ephedrine

Dosage—See preceding article Ephedrine

ABBOTT LABORATORIES

Solution Ephedrine Sulfate 25 mg in 1 cc and 50 mg in 1 cc ampuls

Capsules Ephedrine Sulfate 24 mg and 50 mg

Solution Ephedrine Sulfate 3 per Cent Preserved with chlorobutanol 0.5 per cent

AMERICAN PHARMACEUTICAL CO INC

Solution Ephedrine Sulfate, 3 per Cent 1 fluidounce bottle Preserved with 0.5 per cent chlorobutanol

Capsules Ephedrine Sulfate 25 mg and 50 mg

GEORGE A. BRON & COMPANY, INC

Ephedrine Sulfate 1% Nasal Jelly with Sodium Chloride 15 Gm collapsible tube Ephedrine sulfate 1 per cent with sodium chloride 0.8 per cent in a water soluble boroglycerin jelly base

BURROUGHS WELLCOME & Co., Inc

Ephedrine Sulfate (*Powder*) 15 cc. and 30 cc bottles

Ephedrine Sulfate Injection 49 mg in 1 cc hypodermics

Solution Ephedrine Sulfate, 3 per Cent Preserved with chlorobutanol 0.5 per cent, 1 fluidounce and 1 pint bottles

ENDO PRODUCTS, INC

Solution Ephedrine Sulfate 50 mg in 1 cc ampuls

Tablets Ephedrine Sulfate 24 mg

Solution Ephedrine Sulfate, 3 per Cent 29.5 cc bottle Preserved with 0.5 per cent chlorobutanol

GANE AND INGRAM, INC

Ephedrine Sulfate (*Powder*) bulk

LAKESIDE LABORATORIES, INC

Solution Ephedrine Sulfate 50 mg in 1 cc ampuls

ELI LILLY AND COMPANY

Solution Ephedrine Sulfate 25 mg in 1 cc and 50 mg in 1 cc ampuls

Elixir Ephedrine Sulfate Contains ephedrine sulfate 0.44 Gm in 100 cc in a menstruum composed of alcohol 12 per cent glycerin sucrose and water flavored with gluside oenanthe ether oil of orange oil of coriander oil of caraway oil of lemon oil of cassia oil of anise saffron and vanilla

Ephedrine Jelly Ephedrine sulfate 1 Gm glycerin 15 Gm tragacanth 1 Gm eucalyptol 0.1 Gm oil of wintergreen 10 mg oil of dwarf pine needles 10 mg sodium phosphate U S P 0.16 Gm water to make 100 Gm

Pulvules Ephedrine Sulfate 25 mg and 50 mg

Solution Ephedrine Sulfate 3 per Cent Preserved with chlorobutanol 0.5 per cent

Syrup Ephedrine Sulfate Containing ephedrine sulfate, 0.22 Gm in 100 cc and alcohol 12 per cent it is flavored with vanilla benzaldehyde and tolu and tinted with amaranth

Syrup Ephedrine Sulfate (Double Strength) Containing ephedrine sulfate 0.44 Gm, in 100 cc. and alcohol 12 per cent, it is flavored with vanillin, benzaldehyde and tolu and tinted with amaranth

THE MALTBIE CHEMICAL COMPANY

Ephedrine Nasal Jelly—Ephedrine sulfate, 1 per cent and sodium benzoate 0.5 per cent in a glycerite of tragacanth base

MENCK & CO., INC.

Ephedrine Sulfate (Powder) bulk

THE W. S. MENFELL CO. LOESEN LABORATORY DIVISION

Solution Ephedrine Sulfate 48 mg in 1 cc ampuls

PARKE, DAVIS & COMPANY

Capsules Ephedrine Sulfate 25 mg and 50 mg

Solution Ephedrine Sulfate 50 mg in 1 cc glaseptic ampuls

Solution Ephedrine Sulfate, 3 per Cent Preserved with chlorobutanol 0.5 per cent

SHARP & DOHME, INC.

Solution Ephedrine Sulfate 50 mg in 1 cc ampuls Preserved with 0.5 per cent of chlorobutanol

Capsules Ephedrine Sulfate 25 mg and 50 mg

Solution Ephedrine Sulfate 3 per Cent Preserved with chlorobutanol 0.5 per cent

SMITH DONSEY COMPANY

Capsules Ephedrine Sulfate 25 mg and 50 mg

THE UPJOHN COMPANY

Solution Ephedrine Sulfate 50 mg in 1 cc ampuls

Capsules Ephedrine Sulfate 25 mg and 50 mg

WILLIAM R. WARNER & CO. INC.

Solution Ephedrine Sulfate 50 mg in 1 cc ampul

RACEPHEDRINE—Racemic Ephedrine—d l Ephedrine— $C_{10}H_{15}ON$ —d l γ hydroxy β methylamine phenyl propane

Actions and Uses—The same as those of l ephedrine

Dosage—From 30 to 50 mg

Tests and Standards—

Racephedrine is a colorless crystalline substance. The melting point

Transfer 0.25 Gm. of racephedrine, accurately weighed, and previously dried over phosphorus pentoxide for five hours at room temperature, to a beaker. Add 10 cc. of distilled water and titrate with 0.1 normal sulfuric acid in a slight excess, using methyl red as indicator. Back titrate with 0.1 normal sodium hydroxide. Each cubic centimeter of 0.1 normal sulfuric acid is equivalent to 0.01651 Gm. of anhydrous racephedrine.

GANE'S CHEMICAL WORKS, INC.

Racephedrine (*Crystals*)• bulk

RACEPHEDRINE HYDROCHLORIDE.—Racemic Ephedrine Hydrochloride — *d,l*-Ephedrine Hydrochloride — $C_{10}H_{15}ON.HCl$.

Actions and Uses—The same as those of *l*-ephedrine hydrochloride.

Dosage—From 30 to 50 mg.

Tests and Standards—

Dissolve approximately 0.02 Gm. of racephedrine hydrochloride in 1 cc. of concentrated sulfuric acid; no color is formed. To approximately 0.2 Gm. dissolved in 1 cc. of distilled water add 2 cc. of 20 per cent sodium hydroxide solution; only drops are formed. Extract the milky turbid mixture twice with 25 cc. of ether; the (racephedrine) base crystallizes out on slow evaporation of the ether; after recrystallization from ether and drying at room temperature over phosphorus pentoxide in a slight vacuum, the racephedrine melts at 76° C.

Dissolve approximately 0.2 Gm. of racephedrine in 8 cc. of distilled water, add 1 drop of 2 per cent copper sulfate solution and 1 cc. of 20 per cent sodium hydroxide solution; a purple color is developed which,

on shaking with ether, is partially dissolved in the ether layer; evaporate the ether layer, a pinkish residue remains. Place a drop of a 5 per

equivalent to 0.01651 Gm of anhydrous racephedrine)

GANE'S CHEMICAL WORKS, INC.

Racephedrine Hydrochloride (Crystals): bulk

THE UPJOHN COMPANY

Racephedrine Hydrochloride (Powder): 120 Gm bottles

Capsules Racephedrine Hydrochloride: 25 mg

Racephedrine Hydrochloride 1 per Cent in Ringer's Solution: Contains in each 100 cc racephedrine hydrochloride, N. N. R., 1 Gm, chlorobutanol, 0.5 Gm, sodium chloride, 0.86 Gm, potassium chloride, 30 mg, and calcium chloride, 33 mg dissolved in distilled water

RACÉPHEDRINE SULFATE.—Racemic Ephedrine Sulfate— $C_{10}H_{15}ONH_2SO_4$

Actions and Uses.—The same as those of 1-ephedrine sulfate

Dosage.—From 30 to 50 mg

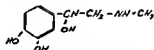
Tests and Standards—

Racephedrine sulfate is a colorless, crystalline substance. The melting point is 247° C (microscopic heating stage). The solubility is fair in water and alcohol. Dissolve 0.5 Gm in 25 cc of distilled water. The solution is neutral to litmus and does not show optical activity.
 weight over
 is not more
 sulfate has
 phedrine, as
 17.5 per cent

GANE'S CHEMICAL WORKS, INC.

Racephedrine Sulfate (Crystals): bulk

EPINEPHRINE—U S P Epinephrine, the active principle of the medullary portion of the suprarenal glands, is extensively used in surgery and to a less extent in medicine in the form of the 1 in 1,000 solution of epinephrine hydrochloride (solution of epinephrine hydrochloride U S P). The alkaloid in addition to being obtained from the suprarenal glands, is also prepared synthetically, and such preparations if they are levorotatory, are equally as active as the natural product. Artificial epinephrines have also been prepared which are optically inactive, and as such are only about half as active physiologically as is natural epinephrine. Dextrorotatory epinephrine is almost inactive.



For description and standards see the U S Pharmacopeia under Epinephrine, Epinephrine Hydrochloride injection and Epinephrine Hydrochloride Spray.

Actions and Uses—Epinephrine acts peripherally on a variety of structures by stimulating the myoneural junctions of the sympathetic nerve endings. Its most important actions consist of a constriction of the blood vessels of the skin, dilatation of blood vessels of the voluntary muscles, stimulation of the heart with an increase in cardiac output, a rise in systolic arterial pressure and a widening of pulse pressure. Relaxation of the bronchial muscles and also glycosuria follow intramuscular or hypodermic injection. Moderate doses when given by mouth

Epinephrine is used locally for its vasoconstrictor action in hemorrhage and in catarrhal and congestive conditions. It often relieves asthmatic paroxysms when used by hypodermic injection, because of the marked increase in vital capacity produced by the drug it is most valuable for treating a severe acute attack of asthma. If however asthmatic paroxysms are frequent it is generally advisable to use ephedrine with or in place of epinephrine. Intravenous injections are sometimes effective in shock and anesthesia accidents (care being taken not to give an overdose). It is of little or no value in Addison's disease. Epinephrine in the form of a 2 per cent solution of a salt of epinephrine has been used locally in the treatment of glaucoma with apparently favorable results in certain cases while in other cases it appears to be ineffective.

Epinephrine is contraindicated in cyclopropane or chloroform anesthesia because of its potential danger as a cardiac stimulant in connection with these drugs.

71

me is used to prolong
retarding the circula
& the removal of the

anesthetic agent by too rapid absorption into the blood stream. In the same manner it is believed to lessen the toxicity of the local anesthetics by retarding their absorption into the general circulation.

Dilute watery solutions rapidly lose their strength the deterioration being accompanied by a reddish or brownish discoloration.

To guard against too great a local ischemia which may lead to local death of tissue the concentration of epinephrine in the local anesthetic solution should not be greater than 1 : 50 000.

To guard against a possible systemic reaction due to absorption of epinephrine the total dose of this drug injected with a local anesthetic solution at one time should never be greater than 1 mg (1 cc).

Dosage—Hypodermically or intramuscularly from 0.06 to 1 cc of a 1 in 1 000 solution of epinephrine hydrochloride. Locally it is used in solution varying in strength from 1 in 15 000 to 1 in 1 000. Epinephrine is also used in solution in ointment for application to mucous membranes such as the eye or the nose where a slower but more lasting action is desired and in suppositories.

THE ARMOUR LABORATORIES

Suprarenalin (Crystals) 63 mg vials Epinephrine

U S patent 829 220 (Aug 21 1906 exp red)

PARKE DAVIS & COMPANY

Adrenalin (Crystals) bulk

U S patents 730 175 730 176 730 196 730 197 730 198 (June 2 1903 exp red) 753 177 (Feb 23 1904 exp red) U S trademark 53 934

Adrenalin Inhalant with Chloretone 3 per Cent A glycerin solution containing 1 part of adrenalin (as adrenalin chloride) in 1 000 3 per cent of chloretone 15 per cent of alcohol and aromatics.

Adrenalin Ointment Contains adrenalin chloride equivalent to one part of adrenalin in 1 000 parts of oleaginous ointment base.

Adrenalin Suppositories One part of adrenalin (as adrenalin chloride) to 1 000 parts of oil of theobroma (cacao butter) and not more than 0.2 per cent of sodium bisulfite. Each suppository weighs about 1 Gm.

Adrenalin Tablets 1 mg Adrenalin as borate yielding a 1 in 1000 solution when dissolved in 1 cc of water. Each tablet contains not more than 1 mg of sodium bisulfite.

Adrenalin Tablets 0.33 mg Each contains adrenalin 0.33 mg as borate yielding a 1 in 1000 solution when dissolved in $\frac{1}{3}$ cc water. Each tablet contains not more than 0.33 mg of sodium bisulfite.

Adrenalin and Cocaine Tablets Each hypodermic tablet contains cocaine hydrochloride 10 mg adrenalin 0.05 mg and not more than 0.33 mg of sodium bisulfite.

Adrenalin Chloride Solution 1:10,000 1 cc ampuls containing sterile solution 1 part of epinephrine hydrochloride in 10,000 parts isotonic solution of sodium chloride with not more than 0.1 per cent of sodium bisulfite as a preservative.

Adrenalin Chloride Solution 1:2,600 1 cc ampuls containing sterile solution 1 part of epinephrine hydrochloride in 2,600 parts of isotonic solution of sodium chloride with not more than 0.1 per cent of sodium bisulfite as a preservative.

THE UPJOHN COMPANY

Epinephrine (Powder) 65 mg vials

WILSON LABORATORIES

Epinephrine (Crystals) bulk

WINTHROP CHEMICAL COMPANY INC

Suprarenin—Epinephrine made synthetically by the method of Stolz and Fletcher (*Ztschr f physiol Chem* vol 58 p 189).

Suprarenin Bitartrate Powder 50 mg ampuls. Each ampul contains suprarenin bitartrate 91 mg equivalent to suprarenin 50 mg.

Suprarenin Bitartrate Solution 1:1,000 1 cc ampuls and 30 cc bottles. Each 1 cc contains suprarenin bitartrate equivalent to suprarenin 1 mg. Chlorobutanol 0.5 per cent is contained in the bulk packages.

Tablets Suprarenin Bitartrate 1 mg Each tablet contains suprarenin bitartrate equivalent to 1 mg of suprarenin.

Tablets Suprarenin Bitartrate 20 mg Each tablet contains suprarenin bitartrate 36.4 mg equivalent to suprarenin 20 mg with lactose 38.5 mg and acetone sodium bisulfite not more than 0.1 mg.

U S patent 986,156 (March 7, 1911 exp red)

SOLUTION OF EPINEPHRINE HYDROCHLORIDE—A solution of epinephrine hydrochloride in distilled water having a potency equivalent to a solution containing 1 Gm of U S P Epinephrine Reference Standard in each 1,000 cc' U S P

For description and standards see the U S Pharmacopeia under Solution of Epinephrine Hydrochloride

Actions and Uses—See Epinephrine

Dosage—See Epinephrine

ABBOTT LABORATORIES

Solution Epinephrine Hydrochloride 1,000 30 cc safety container for parenteral or topical use contains sodium bisulfite 0.1 per cent and chlorobutanol 0.5 per cent as a preservative Also available in 1 cc ampuls containing sodium bisulfite 0.1 per cent as a preservative

THE ARMOUR LABORATORIES

Suprarenalin Solution 1,000 1 cc ampuls 5 cc 10 cc and 30 cc vials for hypodermic use and 30 cc bottles for topical use Contains epinephrine hydrochloride 0.1 per cent chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent in isotonic solution of sodium chloride

GEORGE A. BREON & COMPANY, INC.

Solution Epinephrine Hydrochloride 1,000 1 cc ampuls Contains chlorobutanol 0.5 per cent and sulfurous acid not more than 0.06 per cent in isotonic solution of sodium chloride

BRISTOL LABORATORIES, INC.

Epinephrine Hydrochloride Solution 1,000 1 cc ampuls 10 cc and 30 cc vials for parenteral injection and 30 cc

BURROUGHS WELLCOME & CO., INC.

Solution of Epinephrine Hydrochloride 1,000 30 cc bottle Contains epinephrine hydrochloride 0.1 per cent chlorobutanol 0.5 per cent, potassium metabisulfite 0.1 per cent and sodium chloride in isotonic solution

Hypoid Epinephrine Hydrochloride Injection 1 cc ampuls Contains epinephrine hydrochloride 0.1 per cent chlorobutanol 0.5 per cent potassium metabisulfite 0.1 per cent and sodium chloride in isotonic solution

bottles for topical administration Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as preservatives in isotonic solution of sodium chloride

ENDO PRODUCTS, INC

Solution Epinephrine Hydrochloride, 1:1000 1 cc ampuls and 30 cc vials (rubber stoppered and cork stoppered) Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as a preservative in isotonic solution of sodium chloride

LAKESIDE LABORATORIES INC

Solution of Epinephrine Hydrochloride, 1:1000 1 cc ampuls and 30 cc vials Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as a preservative in isotonic solution of sodium chloride saturated with carbon dioxide

LEDERLE LABORATORIES INC

Sterile Solution Epinephrine Hydrochloride 1:1000 1 cc ampuls and 30 cc vials for parenteral injection Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as preservatives

PARKE DAVIS & COMPANY

Adrenalin Chloride Solution 1:1000 1 cc ampul contains epinephrine hydrochloride 0.1 per cent in isotonic solution of sodium chloride with chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent as preservatives

THE UPJOHN COMPANY

Solution Epinephrine Hydrochloride 1:1000 1 cc ampuls and 30 cc vials Each cubic centimeter contains r dioxide (as nol not more with carbon

U S STANDARD PRODUCTS CO

Epinephrine Hydrochloride Solution 1:1000 1 cc ampuls and 30 cc bottles for topical use Contains chlorobutanol 0.5 per cent as a preservative

WARREN TEED PRODUCTS COMPANY

Sterilized Solution of Epinephrine Hydrochloride 1:1000 30 cc rubber stoppered vials Contains epinephrine hydrochloride 0.1 per cent sodium bisulfite 0.1 per cent and chlorobutanol 0.5 per cent in isotonic solution of sodium chloride.

WILSON LABORATORIES

Solution Epinephrine Hydrochloride 1 1,000 30 cc bottles and vials, for topical use. Contains chlorobutanol 0.5 per cent and sulfurous acid not more than 0.06 per cent as preservatives in isotonic solution of sodium chloride.

SUSPENSION OF EPINEPHRINE IN OIL, 1 500

—Suspension of epinephrine base 1 500. A 0.2 per cent suspension containing 1 part of epinephrine U S P to 500 parts of vegetable oil.

Actions and Uses—Injections of solutions of epinephrine salts (1 1,000) are known to provide prompt but transient relief in the treatment of severe attacks of bronchial asthma by relaxation of the bronchial muscles. Recent evidence indicates that injections of vegetable oil suspensions of epinephrine base (1 500) delay but prolong the action of the drug and thus provide more sustained symptomatic relief in this condition as well as in certain cases of hay fever, urticaria, angioneurotic edema and serum sickness. The usual contraindications to epinephrine must be kept in mind. The preparation should not be given to the aged or to patients with hypertension because of its prolonged pressor effects. Its sustained action may also prolong disagreeable side effects as well as serious reactions due to overdosage in less tolerant individuals. Local reactions due to irritation by

have also been r

it be administered

be paid to the

sites of injection

be partially avoided by adequate resuspension (shaking) of any precipitate in the oil; the use of a dry syringe and needle and precaution to prevent injecting directly into the blood stream by withdrawal of the syringe plunger to determine the location of the needle point in relation to a vessel before each injection and caution in the selection of the initial dose. The use of a small caliber needle to minimize trauma to blood vessels is also recommended. Intravenous injection is of course, contraindicated.

Dosage—Intramuscularly from 0.2 cc to 1.5 cc. (0.4 mg to 3.0 mg epinephrine base) administered every eight to sixteen hours. The initial dose for adults should never exceed 0.5 cc (1 mg epinephrine base) and caution is necessary when subsequent doses larger than 1.0 cc. are employed because of the unusually large amount of active material introduced (1 cc. of the oil suspension 1 500 is the equivalent of 2 cc. of an epinephrine solution 1 1,000) and its more prolonged action. Doses in excess of 1.5 cc. are not recommended.

Tests and Standards—

Epinephrine in oil occurs as a pale yellow to white milky suspension from which a white solid settles out on standing. Centrifugate an ampule of epinephrine in oil until the crystals have collected in the bottom.

open the ampule, decant the clear oil and wash the residue with two 1 cc portions of acetone by decanting on the residue dried at 75°C melts above 215°C when heated at a rate of 8 degrees per minute.

Transfer an accurately measured volume of epinephrine in oil containing approximately 8 mg of epinephrine to a centrifuge tube. Centrifuge, wash and dry as described above. Dissolve the residue in 0.40 cc of normal hydrochloric acid, filter and polarize in a micro-polar scope tube. The specific rotation $[\alpha]_{\text{D}}^{25}$ is between -50.0 and -53.5 degrees.

Shake 10 cc of epinephrine in oil with 5.0 cc of tenth normal hydrochloric acid add 200 cc of distilled water, shake filter through a paper previously moistened with water. Discard the first 5 cc and save the remainder. Add 5.0 cc of tenth normal hydrochloric acid, warm same time prepare adding 5.0 cc of "

in 200 cc of 10% normal hydrochloric acid to 10 cc of peanut oil. Warm the standard and sample solution for fifteen minutes at 38 C, cool to room temperature and compare in a colorimeter. The epinephrine content is not more than 2.15 nor less than 1.85 mg. per cc.

ABBOTT LABORATORIES

Epinephrine in Oil 1 500 1 cc ampuls A suspension of 2 mg of epinephrine in 1 cc of purified peanut oil

ENDO PRODUCTS, INC.

Epinephrine in Oil, 1 500 1 cc ampuls A suspension of 2 milligrams of epinephrine in 1 cc of peanut oil

LAKESIDE LABORATORIES INC

Epinephrine in Oil, 1:500 1 cc ampuls A suspension of 2 mg powdered epinephrine crystals in 1 cc of sesame oil

PARKE, DAVIS & COMPANY

Adrenalin in Oil 1 500 1 cc ampuls A suspension of 2 mg of crystalline epinephrine in 1 cc of peanut oil

SMITH DORSEY COMPANY

Epinephrine in Oil, 1 500 1 cc ampuls A suspension of 2 milligrams of crystalline epinephrine in 1 cc of peanut oil

E R SQUIBB & SONS

Epinephrine in Oil 1 500 1 cc ampuls A suspension of 2 mg of crystalline epinephrine in 1 cc of peanut oil

SOLUTION OF EPINEPHRINE HYDROCHLORIDE 1:100—A solution containing 1 part of epinephrine hydrochloride U S P in 100 parts of isotonic solution of sodium chloride

Actions and Uses—Injections of solutions of epinephrine (1:1000) are known to be useful in the treatment of severe attacks of bronchial asthma. Recent evidence indicates that the oral inhalation of solution of epinephrine ten times stronger than those used by hypodermic injection gives relief in acute attacks of bronchial asthma when other measures fail. The physician should familiarize himself with the procedure before employing it in the treatment of his patients. It is absolutely essential that such treatment be instituted under the supervision of the physician and the patient warned of the dangers of using a solution of such strength carelessly. It is also necessary that the atomizer or nebulizer which is used in the administration of such solutions produce a fine mistlike spray free from minute droplets. Every precaution must be taken to avoid confusion between this solution (1:100) and the official 1:1,000 solution of epinephrine hydrochloride, since the 1:100 solution is not suitable for hypodermic use and should never be employed in that matter.

Dosage—A definite dosage cannot be stated for the use of this preparation. It is obviously essential that the amounts used not exceed the minimal amount which will give effective relief. It is best to start with a single compression of the bulb of the atomizer or nebulizer until it is determined what dosage is adequate and safe. Its use should not be repeated until several minutes have passed so that the full effect of the inhalation can be observed before additional amounts are used.

THE ARMOUR LABORATORIES

Suprarenalin Solution 1:100 A solution of epinephrine hydrochloride 10 per cent, containing chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent as preservatives.

BRISTOL LABORATORIES, INC.

Solution Epinephrine Hydrochloride 1:100 5 cc. Contains epinephrine 10 mg., chlorobutanol 5 mg. and sodium bisulfite 1 mg. as preservative in isotonic solution of sodium chloride.

BURROUGHS WELLCOME & Co., INC.

Solution of Epinephrine Hydrochloride 1:100 5 cc. Contains epinephrine hydrochloride 1 per cent, chlorobutanol 0.5 per cent, sodium bisulfite 0.3 per cent and sodium chloride in isotonic solution.

LAKESIDE LABORATORIES, INC.

Solution of Epinephrine Hydrochloride, 1:100 5 cc. screw capped vials. Each cubic centimeter contains epinephrine

hydrochloride, 0.5 per cent chlorobutanol and 1 per cent sodium bisulfite in isotonic sodium chloride solution saturated with carbon dioxide

PARKE, DAVIS & COMPANY

Strong Solution of Epinephrine Hydrochloride 1:100 5 cc vial Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium bisulfite

PARKE, DAVIS & COMPANY

Solution of Adrenalin Chloride 1:100 5 cc vial A solution of epinephrine hydrochloride 10 per cent, containing chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent as preservatives

KEPHRINE

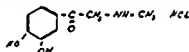
acetocatechol

methylamine

(CH₃)₂ HCl

of a base

catechol) but differs in that kephrine possesses a ketone group in place of the secondary alcohol group of epinephrine



Actions and Uses—Kephrine hydrochloride acts by constriction of the blood vessels. In comparison with epinephrine its action is less powerful but the effects are more lasting. Kephrine hydrochloride is used only locally and will, as a rule, arrest capillary bleeding within two or three minutes. The hemostatic effects usually persist from one to two hours. As there is no appreciable absorption of kephrine hydrochloride into the blood stream it does not have any noticeable effect on the blood pressure. Kephrine hydrochloride is not destroyed by blood alkalis.

Dose—Kephrine hydrochloride is marketed in the form of powder and its proprietary bandages and gauze impregnated with kephrine hydrochloride are also supplied. The selection of a suitable dosage form is governed by the anatomic or pathologic characteristics of the individual case.

Tests and Standards—

Kephrine hydrochloride occurs as a white, odorless powder, freely soluble in water, soluble in alcohol, insoluble in ether. Its aqueous solution is neutral to litmus. Kephrine hydrochloride melts at 214 to 216°C.

It is soluble about 1:100 in water, soluble in 25 cc. of water, slightly soluble in alcohol, soluble in 100 cc. of water, slightly soluble in ether.

methylaminoacetatechol on a filter paper, wash and dry at 100 C. a yellow crystalline powder results which on heating deepens in color at 200 C. and "melts" with decomposition at 230 C.; the filtrate from the foregoing gives a white precipitate with silver nitrate solution, insoluble in boiling nitric acid but soluble in an excess of ammonia water.

Incinerate about 0.5 weighed; the residue is 0.25 Gm. of kephrine b Kjeldahl flask and determine method described in Met Agricultural Chemists, nitrogen is not less than when calculated to the kephrine hydrochloride, flask, add 100 cc. of dioxide, and titrate with phenolphthalein as an indicator corresponds to not less than calculated to the dried as hydrochloride, accurately meyer flask, dissolve in diluted ammonium hydroxide place the flask and contents in a refrigerator at 5 C. and allow to stand for eighteen hours. Collect the precipitate on a tared Gooch crucible, wash with cold water followed by cold alcohol and ether, and dry to constant weight at 100 C. the percentage of methylaminoacetatechol obtained corresponds to not less than 83 per cent, nor more than 86 per cent, calculated to the dried substance.

WINTHROP CHEMICAL COMPANY, INC.

Kephrene Hydrochloride Powder: Kephrene hydrochloride 5 parts and tricalcium phosphate 95 parts

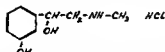
Kephrene Hydrochloride Bandage: Bandages, 5 meters long and 1, 3, 5 and 8 centimeters wide, impregnated with kephrene hydrochloride, 1 Gm. per 3,000 square centimeters.

Kephrene Hydrochloride Gauze: Gauze impregnated with kephrene hydrochloride, 1 Gm. per 3,000 square centimeters

AMPHIPHILIC HYDROCHLORIDE.—laevo-α-
—The hydrochloride

of the laevo isomer of a synthetically prepared derivative of

rine tartrate is a *racemic* compound, and (3) the hydroxyl group of the nucleus in neo synephrine hydrochloride is in the *meta* position—in synephrine tartrate it is in the *para* position



Actions and Uses—Neo synephrine hydrochloride is a vasoconstrictor and is active as a vasopressor when administered orally. It is more powerful in vasoconstrictive ability than synephrine tartrate, and possesses a relatively low toxicity. Applied to mucous membranes it causes contraction of the small blood vessels, thus reducing swelling and congestion of such membranes. Neo synephrine hydrochloride may be useful in

retard the systemic absorption of the anesthetic and to prolong its action by local vasoconstriction. It may be injected alone for vasopressor effects as a preliminary or supportive measure to combat acute hypotension in spinal anesthesia. It may be similarly employed in other acute hypotensive states due to

pupil

Dosage—For topical application to the nasal mucous membrane the 0.25 per cent solution is ordinarily used. The 1 per cent solution diluted with an equal volume of physiologic solution of sodium chloride or Ringer's solution may be used when a stronger preparation is desired. For surgical and dental anesthesia it may be diluted in the proportion of 0.3 to 0.5 cc of the 1 per cent solution to 10 cc of a 2 per cent procaine hydrochloride solution. For parenteral injection

0.1 to 1.0 cc. of the 1 per cent solution. Initial dose should not exceed 0.5 cc (5 mg) and subsequent doses should not be administered at intervals less than 10 to 15 minutes. The intravenous dose when necessary should be about one-tenth the subcutaneous or intramuscular dose. As a mydriatic, one or two drops of the 1 per cent solution or emulsion or the 2½ per cent ophthalmic solution, as a temporary vasoconstrictor in the eye, one drop of the 10 per cent emulsion or the 10 per cent solution. The ¼ per cent ophthalmic solution may be used as a decongestant for minor irritations of the conjunctiva. Preparations of neo-synephrine hydrochloride are incompatible with butyn, but other local anesthetics may and should be used beforehand to reduce the irritation produced by the 10 per cent emulsion. The 2½ per cent ophthalmic solution is not to be used in the eye.

cont

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hydr.

be sterilized by boiling

Tests and Standards—

Neo-synephrine hydrochloride occurs as white odorless nonhygroscopic crystals possessing a bitter taste. It is readily soluble in water and alcohol. The aqueous solution is neutral to litmus paper. It melts between 139-143 C.

Transfer 0.3 Gm of neo-synephrine hydrochloride to a glass container, dissolve in 3 cc of water, add 15 drops of ammonia water and rub the glass container with a glass rod the base that separates when washed with cold water and dried melts at 170-171 C, without decomposition. Determine the nitrogen content of the base by the micro Dumas method the nitrogen found is not less than 8.2 per cent nor more than 8.5 per cent. Dissolve 0.010 Gm of neo-synephrine hydrochloride in 1 cc of water and add 1 cc of copper sulfate solution (10 per cent) followed by 1 cc of sodium hydroxide solution (20 per cent), a reddish purple color forms that is not extracted by ether.

the container and mixture to stand for six hours transfer to a Gooch crucible wash well with diluted nitric acid (10 cc of diluted nitric acid) a desiccator and weigh. The residue of copper chloride weighed is not more than 0.2 per cent. Heat about 0.2 hours in air oven at 103 C. The residue of copper chloride weighed for twenty four hours in air oven at 103 C. is not more than 1 per cent.

Determine the nitrogen content by the micro Dumas method the nitrogen found is not less than 6.6 per cent nor more than 7.0 per cent Transfer about 0.5 Gm. of neo-synephrine hydrochloride, accurately weighed, to a platinum dish, ignite until constant weight is attained the ash is less than 0.2 per cent

NEO-SYNEPHRINE HYDROCHLORIDE ONE PER CENT SOLUTION Trans-
fer 10 cc. of the solution to a 25 cc. vial, add 10 drops of ammonia

and 142 C.

Dissolve the residue in 3 cc. of water, add 10 drops of ammonia water, rub the glass container with a glass rod filter the precipitate wash with cold water on a porous plate the melting point is 169-171 C.

NEO-SYNEPHRINE HYDROCHLORIDE 3/4 PER CENT SOLUTION Follow the assay procedure described for the 1 per cent solution except use a 25 cc. sample

FREDERICK STEARNS & COMPANY DIVISION

Neo-Synephrine Hydrochloride Emulsion 1%: 15 cc bottle Neo-synephrine hydrochloride 1 per cent, sodium benzoate 0.4 per cent in a mineral oil and water emulsion containing acacia, preserved with chlorobutanol 0.5 per cent

Neo-Synephrine Hydrochloride Emulsion 10%: 3 cc bottle Neo-synephrine hydrochloride 10 per cent, sodium benzoate 0.4 per cent in a mineral oil and water emulsion containing acacia, preserved with sodium bisulfite 0.1 per cent, ascorbic acid 1 per cent and chlorobutanol 0.5 per cent

Solution Neo-Synephrine Hydrochloride, 3/8 per Cent 15 cc neo-synephrine hydrochloride 3/8 per cent, sodium chloride 0.1 per cent, boric acid 2.2 per cent with chlorobutanol 0.4 per cent and sodium bisulfite 0.05 per cent as preservatives in an aqueous solution

S-1 - Neo-Synephrine Hydrochloride, 1 per Cent Cent.
29.5 hydro-
chloride sodium
chloride 0.05 per cent and sodium bisulfite 0.1 per cent in distilled water

Solution Neo-Synephrine Hydrochloride, 1 per Cent 29.5 cc, 118.3 cc and 473 cc bottles Neo-synephrine hydrochloride 1 per cent, sodium benzoate 0.1 per cent and sodium chloride 0.5 per cent and sodium bisulfite 0.1 per cent in distilled water

Solution Neo-Synephrine Hydrochloride, 1 per cent. 1 cc ampuls and 5 cc. vials Neo-synephrine hydrochloride 1 per cent, sodium bisulfite 0.10 per cent and sodium chloride 0.6 per cent

Solut 15 cc. n
10 per c
bisulfite 0.1 per cent as preservatives in an aqueous solution

Solu
4 cc n-
10 per
bisulfite 0.1 per cent as preservatives in an aqueous solution

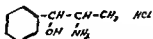
Solution Neo-Synephrine Hydrochloride, 1 per Cent (for Parenteral Use) 5 cc vial and six 1 cc ampuls. A sterile solution of neo-synephrine hydrochloride 1 per cent sodium bisulfite 0.1 per cent and sodium chloride 0.6 per cent in distilled water.

Neo-Synephrine Hydrochloride Jelly, 0.5 per cent Neo-synephrine hydrochloride 0.5 per cent and sodium chloride 0.5 per cent incorporated in a jelly like bland base composed of tragacanth chondrus glycerin and water. Sodium benzoate 0.45 per cent is present as preservative. The product is supplied in collapsible tube containers.

Soluble and sodium menthol and eucalyptol in isotonic solution of three chlorides

U S patent 1932 347 and 1954 389 (April 10 1934 expires April 10 1951) U S trademark 90 142

atomi



Actions and Uses—Propadrine hydrochloride acts similarly to ephedrine. When applied locally in the form of a 1 per cent aqueous solution or 0.66 per cent jelly it produces constriction of the capillaries thereby shrinking the swollen mucous membranes. It is said that its action is somewhat more prolonged than that of ephedrine. It is also claimed that the anxiety complex is not so apt to ensue with propadrine hydrochloride as with ephedrine.

Dosage—As a spray or instillation 1 per cent aqueous solution or application of 0.66 per cent jelly locally orally as

24 mg capsule every two to four hours as indicated. Although no toxic effects have been noted, continued overdosage should be avoided as with other vasoconstrictors.

Tests and Standards—

Propadrine hydrochloride occurs as a white crystalline powder possessing an odor resembling that of benzoic acid. It is freely soluble in water and alcohol, insoluble in ether, chloroform and benzene. Its aqueous solution is neutral to litmus. Propadrine hydrochloride melts at 190-194°C.

Dissolve about 0.5 Gm of propadrine hydrochloride in 25 cc of water and add 5 cc of a saturated solution of sodium carbonate. Cool in an ice bath and collect the resultant needle-shaped crystals on a filter paper, wash and dry at 80 C; the melting point of the α -hydroxy β -amino-propylbenzene is 101-101.5 C.

Dissolve 0.05 Gm. of propadrine hydrochloride in 100 cc. of water separate portions of 2 cc. yield a yellow color with 5 drops of a 9 per cent ferric chloride solution (distinction from cocaine, *ephedrine*, *epinephrine*) no precipitate with potassium mercuric iodide solution (Mayer's reagent) (distinction from *benzedrine*). To about 0.1 Gm. of propadrine hydrochloride in 5 cc. of water add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution no turbidity develops (sulfate).

Dry about 0.3 Gm of propadrine hydrochloride accurately weighed to constant weight at 100 °C the loss in weight does not exceed 1 per cent. Incinerate about 0.3 Gm of propadrine hydrochloride accurately weighed the residue does not exceed 0.5 per cent. Transfer

about 0
300 cc
the met
Official
amount
per cent
Gm of
beaker
as descr
the am
per cent
substance

SHARP & DOHMF, INC

Elixir Propadrine Hydrochloride Each 30 cc contains propadrine hydrochloride 0.13 Gm in a menstruum composed of alcohol 16 per cent glycerin sucrose and water flavored with oil sweet orange fluidextract licorice, and oil ceylon cinnamon and colored with carmoisin (certified) and caramel

Propadrine Hydrochloride Capsules 24 mg and 48 mg

butanol 0.5 per cent is added as preservative

Propadrine Hydrochloride Solution, 1%. An aqueous solution containing 1 per cent propadrine hydrochloride and made isotonic by the addition of 0.58 per cent sodium chloride, chlorobutanol 0.5 per cent is added as a preservative.

Propadrine Hydrochloride Solution, 3%: An aqueous solution containing 3 per cent propadrine hydrochloride and 0.5 per cent chlorobutanol as a preservative.

U. S. patent 1,989,093 (Jan. 29, 1935, expires 1952). Propadrine is a U. S. registered trademark, but the firm disclaims any proprietary rights to the name.

Anti-Sympathomimetic Agents

Drugs exhibiting this action include preparations of ergot which are described in the chapter on ecboles.

Parasympathomimetic Agents

ACETYL-BETA-METHYLCHOLINE

Acetyl beta methyl choline

Effect. It exerts a depressant effect at the sinoauricular node, auricular musculature and auriculoventricular node and bundle of the heart and stimulates gastrointestinal peristalsis. The bradycardia induced by the drug is blocked by quinidine, which also antagonizes its prolongation of auriculoventricular conduction. It also produces a general vasodilatation of blood vessels which are not known to be innervated by parasympathetic nerves, with a subsequent fall in blood pressure. The drug may therefore be compared to epinephrine. All its actions are rapid and its effects are quickly eliminated.

Unlike acetylcholine, the drug is capable of exerting a physiological effect when administered orally. When injected subcutaneously its actions appear to be more prolonged than those of acetylcholine, although the effect on the heart rate and blood pressure persists for only a few minutes. Its intravenous injection is dangerous.

Crystalline water soluble salts of the base, acetyl beta methylcholine, are employed to produce the effects of the drug. The salts are more or less hygroscopic, and if this tendency is extreme, as in the case of the chloride, the crystals must be protected from atmospheric moisture until placed in solution. Acetyl beta methylcholine chloride is therefore not suitable for oral administration in crystalline form but should be given in solution. The entire contents of containers of this salt should be put into solution immediately when these are once opened. Solutions of acetyl beta methylcholine chloride are fairly stable and will keep for at least two or three weeks. They are relatively stable to heat and may be refrigerated to delay mold growth.

U. S. trademark

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... doses are required
... 2 Gm. (10 tabs)
... treatment should
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scleroderma and Raynaud's disease the larger doses are required. With patients in whom a total daily dose of 2 Gm. (10 tablets) of the drug is not effective, the oral method of treatment should be abandoned in favor of the use of mecholyl chloride by subcutaneous administration or local application by the method of ion transfer (iontophoresis).

Tests and Standards —

Mecholyl bromide occurs as a white, crystalline, very hygroscopic powder possessing a slight fishy odor, readily soluble in water and alcohol, insoluble in benzene and ether. The aqueous solution is neutral to litmus. Mecholyl bromide melts at 147-149 C.

Dissolve about 1 Gm. of mecholyl bromide in 10 cc. of water, to a 1 cc. portion add 1 cc. of alcohol and 1 cc. of sulfuric acid and heat in a steam bath; the odor of ethyl acetate becomes perceptible, to another 5 cc. portion add 2.5 Gm. of potassium hydroxide and heat (odor of trimethylamine is noticed); to the remaining portion add an excess of silver nitrate solution (a white, curdy precipitate soluble in ammonia water results). Add 3 cc. of a 20 per cent aqueous solution of sodium perchlorate to 2 cc. of a 10 per cent solution of mecholyl bromide, shake thoroughly and cool in ice water; no precipitate is formed (acetylcholine). Moisten about 0.1 Gm. of mecholyl bromide with a 5 per cent solution of platinum chloride; small rhomboidal plates are formed (distinction from acetylcholine chloride, which forms needles and choline chloride which forms no crystals). Dissolve 0.2 Gm. of mecholyl bromide in 2 cc. of sulfuric acid; the solution is colorless (readily carbonizable substances).

Dry about 0.5 Gm. of mecholyl bromide, accurately weighed, to constant weight at 110 C; the loss in weight does not exceed 13 per cent. Incinerate about 0.5 Gm. of mecholyl bromide, accurately weighed, in a platinum crucible; the residue does not exceed 0.1 per cent. Transfer about 0.5 Gm. of mecholyl bromide, previously dried at 105 C to 110 C, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in Methods of Analysis of the Association of Official Agricultural Chemists; the percentage of nitrogen is not less than 5.6 nor more than 5.9.

Dissolve about 0.4 Gm. of mecholyl bromide, previously dried at 105 C to 110 C and accurately weighed, in 15 cc. of water in an Erlenmeyer flask, add 40 cc. of tenth normal sodium hydroxide solution and heat on the steam bath for forty-five minutes, stopper and allow to cool, titrate the excess of sodium hydroxide with tenth normal hydrochloric acid, using phenolphthalein as an indicator; the amount of acetyl ($\text{CH}_3\text{CO}-$) is not less than 17.5 per cent nor more than 18.3 per cent.

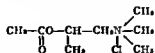
Transfer about 0.4 Gm. of mecholyl bromide, previously dried at 105 C to 110 C and accurately weighed, to a 100 cc. volumetric flask, dissolve in 50 cc. of water, with agitation add 30 cc. of tenth normal silver nitrate solution, add 5 cc. of nitric acid, and finally add water to final volume and mix thoroughly. Filter through a dry filter into a dry flask, rejecting the first filterful, titrate 50 cc. of the filtrate with tenth normal ammonium thiocyanate solution using ferric alum as an indicator; the amount of bromine is not less than 32.9 per cent nor more than 33.5 per cent.

MENCK & CO., INC.

Mecholyl Bromide Tablets: 0.2 Gm.

U S patent 2 040 146 (May 12 1936, expires 1953) U S trademark 318 783

MECHOLYL CHLORIDE—Acetyl beta methylcholine chloride—Trimethyl beta acetoxyl propyl ammonium chloride—The acetyl ester of beta methylcholine chloride having the following formula



Actions and Uses—Mecholyl chloride is useful in the treatment of selected cases of paroxysmal auricular tachycardia not responding to the usual therapeutic measures by subcutaneous injection only in the palliative local treatment of chronic rheumatoid (atrophic) arthritis by the method of ion transfer

tion when the former cannot be employed For the prevention of attacks of paroxysmal auricular tachycardia the drug is inferior to quinidine It is of no apparent value in the treat

abdominal distention atonic constipation pelvic inflammation functional dysmenorrhea atrophic rhinitis glaucoma and hypertension are not warranted on the basis of existing clinical evidence. (Also see preceding article Acetyl Beta Methylcholine)

Dosage—Considerable variation in the oral dosage requirements is to be expected because mecholyl chloride is to some extent destroyed by the gastric juice The therapeutically effective oral dose usually ranges from 0.2 to 0.5 Gm two or three times a day administered by dissolving in a little water which may be added to milk to disguise the bitter taste In overcoming vascular spasm due to moderate exposure to cold oral doses of from 50 mg to 0.1 Gm have been found to be effective In Raynaud's disease scleroderma and ulcers the effective oral dose may be somewhat higher

The subcutaneous dose should be limited to 10 mg on the first injection to test the patient's tolerance If well tolerated the dose may be cautiously increased up to 25 mg This dose is usually adequate for injection when this method of administration is employed in the treatment of Raynaud's disease scleroderma chronic ulcers and other vasospastic conditions of the extremities In paroxysmal auricular tachycardia from 20 mg to 40 mg is injected subcutaneously If a second injection is required it is advisable to wait about ten to twenty minutes until the effect of the first has disappeared and then

only after cautious gentle massage at the site of the first injection. Cumulative, or overdosage, effects may be quickly abolished by an injection of atropine sulfate 0.6 mg.

For application of mecholyl chloride by the method of ion transfer (iontophoresis) it is customary to use a 0.2 to 0.5 per cent (1:500 to 1:200) solution of the drug in distilled water. The solution is applied by moistening the positive electrode fabric which is placed over or near the part to be treated. The strength and duration of the galvanic current regulates the dosage and should always be applied gradually and within the point of comfortable tolerance by the patient. The patient should be instructed to report any sensation of excessive heat or burning. If this occurs the treatment should be stopped and an inspection made to determine if an electrode is improperly placed. The initial treatment should not exceed 5 to 10 milliamperes for thirty minutes. Subsequent treatments usually require from 25 to 30 milliamperes applied for twenty to thirty minutes. Each treatment should be restricted to a limited area such as one hand or one joint when several parts are involved. Three or four days is considered the most satisfactory interval between treatments. The number of treatments necessary to obtain results varies with the patient and with the type of lesion. In Raynaud's disease and scleroderma, ten or more treatments may be necessary to secure improvement, in chronic rheumatoid arthritis the treatments may be reduced to intervals of a week after the first four to six treatments, in varicose indolent and gangrenous ulcers, treatments may be given daily at the start to promote granulation of tissue and then reduced after the first few treatments to two or three times a week. During treatments by ion transfer (iontophoresis) the patient should be covered and protected from drafts and for about thirty minutes after each treatment should remain quiet and be kept warm before being permitted to resume protected activity.

Idiosyncrasy to mecholyl chloride may result in difficulty in breathing. If this is noted the treatment should be stopped and the patient raised to a sitting position. If untoward symptoms do not subside atropine sulfate should be given hypodermically at once.

Tests and Standards—

Mecholyl chloride occurs as a white, crystalline very hygroscopic powder, possessing a slight odor, readily soluble in water and alcohol insoluble in benzene and ether. The aqueous solution is neutral to litmus. Mecholyl chloride melts at 168 to 171°C.

Dissolve about 1 Gm of mecholyl chloride in 10 cc of water, to a 1 cc portion add 1 cc of alcohol and 1 cc of sulfuric acid and heat in a steam bath (odor of ethyl acetate becomes perceptible) to another 5 cc portion add 2.5 Gm of potassium hydroxide and heat (odor of trimethylamine is noticed) to the remaining portion add an excess of silver nitrate solution (a white curdy precipitate soluble in ammonia water results). Add 3 cc of a 20 per cent aqueous solution of sodium perchlorate to 2 cc of a 10 per cent solution of mecholyl chloride shake thoroughly and cool in ice water no precipitate is formed (acetylcholine). Moisten about 0.1 Gm of mecholyl chloride with a 5 per cent solution of platinum chloride small rhombohedric

plates are formed (distinction from acetylcholine chloride which forms needles and choline chloride which forms no crystals) Dissolve 0.3 Gm. of mecholyl chloride in 2 cc. of sulfuric acid the solution is colorless (readily carbonizable substances)

more than 22.3 per cent

Transfer about 0.4 Gm. of mecholyl chloride previously dried at 100 cc. volumetric flask 30 cc. of tenth normal and finally add water enough a dry filter into a 1 cc. of the filtrate with sing ferrie alum as an less than 17.9 per cent

MERCIC & Co, INC

Mecholyl Chloride (Crystals) 1 Gm and 10 Gm bottles for the preparation of solutions for oral administration and for ion transfer (iontophoresis)

U S patent 2 040 146 (May 12 1936 expires 1953) U S trade mark 318 783

Mecholyl Chloride (Crystals) 25 mg sealed ampul for the preparation of solutions for subcutaneous injection

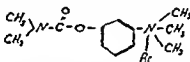
NEOSTIGMINE

Pharmacologic experiments indicate that the neostigmine component of neostigmine compounds possesses some of the properties of the closely allied drug physostigmine. Its actions and uses therefore are similar to those of physostigmine over which it has the advantage of being more stable. Apparently it is as active as physostigmine in stimulating intestinal peristalsis and has a similar but somewhat diminished miotic activity. There is no satisfactory evidence that the symptoms are any less severe with neostigmine or physostigmine or that it is important when used by subcutaneous and intramuscular injection, since the neostigmine component is from four to six times as toxic as physostigmine.

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antidote to ' ' ' ' used for
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lature, and for the symptomatic control of myasthenia gravis.
Their use for the prevention and treatment of intestinal and
bladder atony is based on activity as a vagotonic agent their
anti curare like action is the basis of application in the symp
tomatic treatment of myasthenia gravis The drug is also
credited with mild laxative action but its use solely for that
purpose is not advisable

Neostigmine is available only in the form of its salts

NEOSTIGMINE BROMIDE—U S P—Prostigmine
Bromide— When dried for 6 hours at 100° C contains not
less than 98 per cent of $C_{10}H_{15}BrN_2O_2$ U S P



For description and standards see the U S Pharmacopeia
under Neostigmine Bromide and Neostigmine Bromide Tablets

Actions and Uses—See Neostigmine Neostigmine bromide
is used for the oral treatment of myasthenia gravis The bro
mide is used in the oral tablet form as it is comparatively non
hygroscopic

Dosage—15 mg three times daily If necessary the dose
may be cautiously increased to 30 mg three times daily

HOFMANN-LAROCHE INC

Prostigmine Bromide Tablets 0015 Gm

U S patent 1 905 990 (April 25 1933 expires 1950) U S trade
mark 293 869

NEOSTIGMINE METHYLSULFATE—U S P—
Prostigmine Methylsulfate— When dried at 100 C for 6 hours
contains not less than 98 per cent of $C_{10}H_{15}N_2O_2S$ U S P

For description and standards see the U S Pharmacopeia
under Neostigmine Methylsulfate and Neostigmine Methyl
sulfate Injection

Actions and Uses—See Neostigmine

Dosage—Prevention of postoperative distention small doses
of the 1 : 4 000 solution are administered subcutaneously or intra
muscularly at frequent intervals Injections are begun twenty
four hours before the operation if feasible otherwise as soon
as possible and repeated in 1 cc doses every four to six hours
until the second or third postoperative day Treatment of post
operative distention usually one or two ampuls of the 1 : 2 000
solution as required are administered subcutaneously or intra

muscularly. Experimental use in the treatment of myasthenia gravis: only one ampul of the 1:2000 solution is administered initially; the size and interval of the subsequent doses to be given as indicated by the degree and duration of the response to the initial dose. The course of treatment usually consists of from one to four ampuls (from 0.5 to 2 mg. of neostigmine methylsulfate).

HOFFMANN LAROCHE INC.

Solution Prostigmine Methylsulfate 1:2000 and 1:4000
1 cc. ampuls

U. S. patent 1,905,990 (Apr. 25, 1933; expires 1950). U. S. Trade
mark 293,889.

Anti-Parasympathomimetic Agents

ATROPINE DERIVATIVES AND ANALOGUES

Synthetic Mydriatics

The usefulness of atropine is somewhat diminished by the fact that it affects simultaneously so many organs; on the eye its effects continue much longer than is in many cases desirable. Many attempts have been made to secure drugs of the atropine type with more specific actions or drugs that have a more transitory effect upon the eye. One of these drugs (homatropine) is a synthetic alkaloid analogous to atropine; the only difference being that it contains mandelic acid instead of tropic acid in combination with tropine. Eucatropine is a combination of mandelic acid and a base similar to that contained in beta-eucaine.

EUCATROPINE HYDROCHLORIDE—Euphthalmine Hydrochloride—When dried over sulfuric acid for 4 hours contains not less than 86 per cent and not more than 89 per cent of eucatropine ($C_{17}H_{21}NO_3$). U. S. P.

For description and standards see the U. S. Pharmacopeia under Eucatropine Hydrochloride.

Actions and Uses—Eucatropine hydrochloride produces prompt mydriasis free from anesthetic action, pain, corneal irritation or, in normal individuals, increase in intra-ocular tension. It should be noted, however, that eucatropine hydrochloride shares with other mydriatics the hazard of precipitating glaucoma in anatomically predisposed individuals. It has little or no effect on accommodation and such effect as it has disappears more rapidly than that of atropine, cocaine, homatropine, etc. In its effects on the general system eucatropine hydrochloride very closely resembles atropine. It is useful as an aid in ophthalmoscopic examination in place of atropine, homatropine, etc.

Dosage—From 2 to 3 drops of from 5 to 10 per cent solution, according to the age of the patient and the nature of the case, are instilled into the eye

SCIHERING & GIATZ, INC

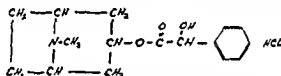
Euphthalmine Hydrochloride (Powder) 0.5 Gm., 5 Gm., and 25 Gm

U S patent 663 754 (expired) U S trademark 35 541

WEINER DRUG & CHEMICAL CO

Eucatropine Hydrochloride (Powder) bulk, 0.5 Gm 1 Gm, 3.54 Gm, 5 Gm and 28.35 Gm

HOMATROPINE HYDROCHLORIDE—Homatropinae Hydrochloridum— $C_{16}H_{21}O_2NHCl$ —The hydrochloride of the alkaloid homatropine, obtained by the condensation of tropine and mandelic acid



Actions and Uses—Homatropine hydrochloride is given for the same indications as the hydrobromide

Dosage—It is applied to the eye in 1 per cent solution

Tests and Standards—

Homatropine hydrochloride occurs as small white crystals soluble in water and alcohol and melting at from 216 to 217 C.

The color test for the identification of homatropine hydrochloride and the tests showing the absence of impurities should agree with those described in the U S Pharmacopeia under homatropine hydrobromide

MERCK & CO, INC

Homatropine Hydrochloride (Crystals) bulk

NOVATROPINE—Homatropinemethylbromide— $C_{16}H_{21}O_2NCH_3Br$ —The methylbromide of the alkaloid homatropine

Actions and Uses—Novatropine is proposed for use in the treatment of gastrointestinal spasm and hyperchlorhydria. Animal experimentation has shown it to be less active than atropine but also less toxic

Dosage—Adults one or two tablets three times daily before meals, children and infants according to age

Tests and Standards—

Novatropine occurs as an odorless, white crystalline powder, possessing a bitter taste, soluble in water and alcohol but insoluble in ether. It melts between 191 and 192 C., with slight decomposition. Aqueous solutions (1 in 50) are neutral to litmus.

Dissolve about 0.5 Gm. of novatropine in 25 cc. of distilled water, separate portions of 2 cc. are not precipitated by 1 cc. portions of sodium carbonate solution, sodium hydroxide solution, or trinitrophenol solution (distinction from most of the alkaloids of atropine type) but are precipitated by 1 cc. portions of potassium mercuric iodide solution, iodine and potassium iodide solution, and a 15 per cent solution of silicomolybdic acid. Add a few drops of nitric acid to about 0.05 Gm. of novatropine, evaporate the mixture to dryness on the water bath, cool the residue and add a few drops of alcoholic potassium hydroxide solution the residue does not become violet colored (distinction from atropine, hyoscyamine and scopolamine).

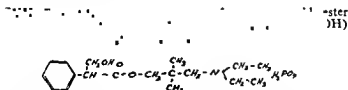
Add 0.5 cc of ammonia to 1 cc of an aqueous solution of novatropine (1 in 100), shake the mixture with chloroform, remove the aqueous layer, and evaporate the chloroform solution to dryness on the water bath. Warm the residue so obtained with about 15 cc of a solution made by dissolving 1 Gm of mercury bichloride in 50 cc of a mixture of 5 volumes of alcohol and 3 volumes of distilled water; it does not develop a yellow or red color (distinction from *homatropine hydrobromide*, *atropine* and *hyoscyamine*).

Incinerate about 0.5 Gm of novatropine, accurately weighed, the ash amounts to not more than 0.1 per cent. Dry about 0.5 Gm of novatropine to constant weight at 100 C the loss in weight does not exceed 0.1 per cent. Transfer about 0.3 Gm of novatropine, accurately weighed, to a 500 cc Kjeldahl flask and determine the nitrogen content according to the method described in Methods of Analysis of the Association of Official Agricultural Chemists, fourth edition, page 23 art 19 the amount of nitrogen is not less than 3.7 per cent, nor more than 3.85 per cent. Transfer about 0.3 Gm of novatropine, accurately weighed, to a 400 cc beaker and determine the bromide content according to the method described in Methods of Analysis of the Association of Official Agricultural Chemists, fourth edition, page 131 art 35 the amount of bromide found corresponds to not less than 21.3 per cent, nor more than 21.9 per cent.

CAMPBELL PRODUCTS, INC.

Novatropine Tablets: 25 mg

U S trademark 240 S37



Actions and Use — Similar to those of atropine directly on smooth on parasympathetic — as actively as atropine or induce mydriasis as readily, and

MERCK & Co, INC

Scopolamine Hydrobromide Crystals* 65 mg, 0.3 Gm and 1 Gm vials

Scopolamine Hydrobromide Powder 65 mg, 0.3 Gm and 1 Gm vials

SCOPOLAMINE STABLE—Scopomannit—An aqueous solution of pure scopolamine hydrobromide, protected against decomposition by the addition of 10 per cent of mannite

Actions Uses and Dosage—The same as those of scopolamine hydrobromide U S P

Tests and Standards—

Scopolamine stable Roche is prepared by dissolving in an aqueous 10% solution of mannite freshly manufactured scopolamine hydrobromide having an optical activity of $[\alpha]_{D}^{15} = -26.0^{\circ}$ (determined in an aqueous solution containing the equivalent of 4.5 Gm of anhydrous scopolamine hydrobromide in 100 cc at a temperature of 15 C in a 100 millimeter tube) The melting point of scopolamine hydrobromide is 195 C

That scopolamine stable Roche contains all of its scopolamine in an antagonistic to both muscarine and pilocarpine

HOFFMANN LAROCHE, INC

U S trademark 103 288 and 103 289

Solution Scopolamine Stable* 0.3 mg in 1 cc and 0.6 mg in 1 cc ampuls Each cubic centimeter contains 0.3 mg of scopolamine hydrobromide in a 10 per cent aqueous solution of mannite

CHAPTER IX

CARDIOVASCULAR AGENTS

Digitalis and Digitalis-like Principles and Preparations

The digitalis group embraces many crude drugs and proximate principles which have a peculiar action on cardiac muscle. *Digitalis strophanthus* and *squill* have been investigated far more than the others and we are much better informed concerning their actions from them are derived nearly all the active principles and proprietary preparations of the group which have been included in N N R.

Digitalis and digitalis like principles may be administered by mouth by injection and as described under the accepted preparations. U S P XII recognizes a solution of digitalis for injection but it should be remembered that the optimum frequency of repetition of the intravenous dose of different digitalis preparations varies widely even with those of equal potency, depending several factors especially on difference in persistence of action. The physician must learn the proper intravenous dosage of any preparation of digitalis which he employs.

Cardiac Action—The cardiac action of the individual drugs of the group is similar. They all act directly on heart muscle to increase its systolic force. The margin between therapeutic and toxic actions on the heart is believed by some to differ for different substances although the weight of evidence indicates that the margin of safety does not differ. In patients with auricular fibrillation they all slow the heart rate by a combination of a direct action on the heart muscle and an indirect vagal action. The larger the dose the more pronounced the direct action. The proportion of these two actions is similar for the different members of the whole group.

Differences exist chiefly in relation to their absorption from the gastrointestinal tract their speed of elimination and their local emetic action. Their potencies differ and difficulties arise from faulty standardization.

Standardization—There are various methods for the standardization of this group of drugs involving the use of several species of animals the frog the guinea pig etc. The U S Pharmacopoeia 12th Revision requires that digitalis be standardized against the U S P Digitalis Reference Standard (1942) by the official cat method which involves intravenous injection into cats until death occurs by cardiac arrest. The available evidence indicates that the cat method yields results more nearly applicable to man than those of the frog method. The Standard preparation and the unknown are similarly injected into groups of animals and the average fatal doses of

the two are compared. The unknown is then adjusted so that 0.1 Gm. has the potency of 0.1 Gm. of the Standard or 1 U. S. P. Digitalis Unit. Since the U. S. P. Digitalis Unit is the result of an assay by the cat method and represents an improved technique in bioassay, the expression of potency in U. S. P. Digitalis Units is preferable to the older expression in terms of 'cat units'.

In the case of digitalis leaf and the tincture, the results of comparison by means of the cat method agree fairly satisfactorily with similar comparisons in humans to whom the drugs are given by oral administration but there is less agreement in the case of purified materials because of wide differences in their absorption from the gastrointestinal tract, and the intravenous method does not distinguish absorbable from nonabsorbable material. Hence a U. S. P. Unit of different specimens of the Digitalis Leaf or Tincture Digitalis may be counted upon to produce substantially similar results when given orally to man (although there are some exceptions), but not so in the case of purified materials.

By direct testing it has been found that 1 U. S. P. Digitalis Unit is equivalent approximately to 1.3 'cat units' using the cat method technique of the Pharmacopeia.

Differences in Emetic Action—The digitalis principles are irritant to mucous membranes and subcutaneous tissues. When given in large doses, the local irritation in the gastrointestinal tract may be sufficient to cause nausea and vomiting within several minutes to an hour or two. These drugs, however, are rarely administered in such doses, and when given in the usual smaller doses the local irritant action is insufficient to cause nausea or vomiting. The nausea or vomiting which follows the customary doses of digitalis is due to a systemic action after absorption and represents a toxic symptom. The seat of this action is the vomiting center through the heart. The emetic action is roughly proportional to the cardiac effects of the various members of the group and when this undesired action is induced it cannot be avoided by changing the mode of administration or by resorting to other members of the group. In such a case the patient is overdigitalized and there is need for reducing the size of the dose.

Differences in Absorption—Digitalis contains a mixture of glycosides, some of which are rapidly, and others poorly absorbed from the gastrointestinal tract. After an oral dose only about one fifth of the potent materials produce a systemic action, as shown by the fact that it requires only about one fifth as much for intravenous as for oral administration to produce the same results. Digitaline Nativelle (digitoxin) is almost completely absorbed whereas other fractions may not be absorbed at all. The potent principles of *Strophanthus* are so poorly absorbed

from the gastrointestinal tract that they are undesirable for oral administration and are used chiefly by intramuscular or intravenous injection in small doses

Differences in Cumulative Action—All the digitalis bodies in common use are cumulative. Not all show the same degree of cumulation, however, due to the fact that some are more rapidly eliminated than others. The cumulative action is especially pronounced in the case of digitalis leaf and digitaline Nativelle (digitoxin). It is much less in the case of strophanthus and strophanthin.

Intravenous Use—The frequency of repetition of the intravenous dose of different digitalis preparations varies widely even with those of equal potency, depending on several factors especially on difference in persistence of action. The physician must learn the proper intravenous dose of any preparation of digitalis which he employs.

Digitalis Principles and Preparations

The disadvantages of all the drugs of the digitalis group have served as a constant stimulus in the search for pure prin
in a potent on

from the gastrointestinal tract would make it possible to digitalize rapidly by oral administration without the danger of local irritant action. Several glycosides of purity such as digitoxin. Many preparations, however, are mixtures of glycosidal materials such as digitolin or digitalen.

Proprietary Digitalis Preparations—Several digitalis preparations have been introduced into therapeutic use with the claim that they are composed either of pure principles or of purified extracts of digitalis and that they are devoid of certain disadvantages possessed by the preparations of the U. S. Pharmacopeia. The Council urges on clinicians the necessity of acquiring skill in the use of digitalis materials by the careful observation of a very few members of the group rather than to try to use without discrimination the large number of preparations which are offered.

DIGITALIS —Foxglove — Digitalis is the dried leaf of *Adonis vernalis*. The potency is 1 Gm. = 1 Int.

U S P

Note—When Digitalis is prescribed Digitalis Pulverata is to be dispensed U S P

For description and standards see the U S Pharmacopeia under Digitalis, Digitalis Capsules, Powder Digitalis, Digitalis Injection, Digitalis Tablets and Tincture of Digitalis

Actions, Uses and Dosage—See Useful Drugs

DIGALEN—The cardioactive principles of digitalis as isolated by Cloetta. It is standardized by the intravenous cat method of Hatcher and Brody (*Am J Pharm* 82:360, 1910).

Actions and Uses—The same as those of digitalis

Dosage—The average dose of digalen (in 30 cc vials) is from 1 to 2 cc. The maximum daily dosage is 6 cc. The average dose of tablets digalen is from ½ to 1 cat unit three times daily. The average dose of digalen injectable is 2 cc.

Preparation —

The dried and finely powdered leaves of digitalis are extracted with

Tests—

Dgalen is a colorless or slightly yellowish liquid of an agreeable aromatic odor with a sweet taste which subsequently becomes bitter.

The active derivative contained in digalen is an amorphous white

residue in about 2 cc. of glacial acetic acid containing a trace of ferric chloride. To this solution add strong sulfuric acid with mixing so as to form a separate layer. A brown ring forms between the two layers which becomes broader after some hours and expands toward the top in a blue green to black shade and toward the bottom in a reddish brown one. The acetic acid finally acquires a dark green blue color.

HOFFMANN LAROCHE, INC.

Solution Digalen Injectable 2 cc ampuls Each 2 cc. represents 1 cat unit in 8 per cent alcohol equivalent in potency to approximately 81 mg U S P Digitalis Reference Standard (1942) = 0.8 U S P NH Digitalis Unit

Solution Digalen 30 cc vials. Each 1 cc represents 1 cat unit in 26 per cent alcohol equivalent in potency to approximately 81 mg U S P Digitalis Reference Standard (1942) = 0.8 U S P M Digitalis Unit.

Tablets Digalen 3/5 cat unit and 1 cat unit respectively equivalent in potency to 40 mg U. S. P. Digitalis Reference

Standard (1942) = 0.4 U S P XII Digitalis Unit and 81 mg U S P. Digitalis Reference Standard (1942) = 0.8 U S P XII Digitalis Unit

U S trademarks 43,593 and 83,738

DIGIFOLIN—A digitalis preparation containing the therapeutically desirable constituents of digitalis leaf. It is standardized by the Digitalis assay method U S P XII.

Actions and Uses—The same as those of digitalis.

Dosage—In the majority of cases in which digitalis therapy is indicated, the oral administration of 0.1 Gm. in the form of tablets, or of 1 cc. of digifolin oral solution four times daily until the desired therapeutic effects or minor toxic symptoms appear. In cases in which the patient has received no digitalis during the preceding two weeks and it is desired to use the massive dose method, digifolin tablets or digifolin oral solution, in the proportion of the former representing 0.7 Gm. of digitalis or 8 cc. of the latter per 45.4 Kg. of the patient's body weight may be employed as the initial dose. If neither clinical improvement nor toxic signs have appeared in six hours, a second dose may be given, one half the size of the initial one, and at the expiration of each succeeding of desired therapeutic effects may be repeated, the third, the fourth, and all subsequent doses being one half that of the third, until the total dosage of the tablets amounts to the equivalent of 1.5 Gm. of digitalis or 16 cc. of the oral solution per hundred pounds of the patient's weight. The intravenous dose of digifolin recommended is 0.03 cc. of the contents of the ampule per pound of body weight in patients who have received no digitalis medication during the preceding two weeks. In the absence of therapeutic effects or signs of digitalis poisoning at the expiration of two hours, 0.0176 cc. per Kg. of body weight may be injected, and further doses of 0.0176 cc. per Kg. of body weight may be injected intravenously at two hour intervals until improvement occurs, poisoning becomes apparent or a total dosage of 0.132 cc. per Kg. of body weight has been reached. Under no circumstances should this dosage be exceeded in seriously ill patients.

Attention is called to the fact that Digifolin provides the active glycosides more than do the whole leaf preparation. Digifolin is responsible for a 20% greater equal unitage than the whole leaf preparation. Digifolin administered orally will, therefore, be found more active than indicated by the potency value obtained by the U S P XII Cat Assay Method. However, as far as the Digifolin ampul solution for intravenous injection is concerned, the experimentally established potency will hold true under clinical conditions also.

Transfer about 0.2 Gm. of digilanid dried under vacuum and accurately weighed to a 250 cc separator add 100 cc of chloroform, 20 cc of methanol and 100 cc of water and shake at 25 C for one minute. Separate the layers and evaporate each in vacuo to dryness. Wash the residues into tared weighing bottles with methanol and again evaporate to dryness in vacuo at 55 C and weigh. The weight of the residue from the chloroform divided by the sum of the weights of the residues is not less than 0.60 and not more than 0.65.

SANDOZ CHEMICAL WORKS, INC

Solution Digilanid 2 cc ampuls (For Intramuscular Use) Each ampul contains 0.4 mg of digilanid equivalent to 1.2 cat units of digitalis.

Solution Digilanid 4 cc ampuls (For Intravenous Use) Each ampul contains 0.8 mg of digilanid equivalent to 2.4 cat units of digitalis.

Solution Digilanid 30 cc vials Each 1 cc contains 0.33 mg of digilanid equivalent to 1 cat unit of digitalis.

Suppositories Digilanid. 0.5 mg (1.5 cat units)

Tablets Digilanid 0.33 mg (1 cat unit)

U S patents 1923 490 (Feb 19 1931 expires 1948) and 1923 491 (Aug 22 1931 expires 1948) U S trademark 291 301

DIGIPOTEN—A mixture of the digitalis glucosides in soluble form diluted with milk sugar to give the preparation an activity equal to that of digitalis of standard quality as determined by the U S Pharmacopeia. It is standardized by the U S P intravenous cat method. Activity is expressed in U S P digitalis units. It is virtually free from digitosaponin.

Actions and Uses—Digipoten has the same activity as digitalis leaf of good quality and may be used as is the official drug with respect to indications and dosage.

Dosage—The same as that of digitalis.

Preparation—

Digipoten is prepared by extracting digitalis leaves with diluted alcohol the alcohol being removed by distillation in vacuo the resulting extract filtered and the filtrate precipitated with tannin. The precipitated tannates of the glucosides are washed with water, and the glucosides are liberated in the usual manner. The resulting green brittle powder is triturated with sufficient milk sugar to reduce the activity of the finished product to the standard.

Tests—

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ABBOTT LABORATORIES

Digipoten Capsules: 01 Gm, (1 U S P unit)

Digipoten Tablets: 50 mg ($\frac{1}{2}$ U S P unit)

DIGITALIN, "GERMAN" —

—A mixture of glucosides according to the process of digitonin, with true digitalin.

NOTE—Digitonin is given as a synonym for crystallized digitalin by some manufacturers, and it is to be observed particularly that this is quite different from "true digitalin" or the "crystalline digitaline" of the French Pharmacopœia

Actions and Uses—These are similar to those of digitalis

Dosage—What has been said of the uncertainty of dosage of true digitalin must obviously apply with even greater force to "German" digitalin, since the activity of the latter probably depends mainly on the true digitalin that it contains. The dose of "German" digitalin was formerly given as 0.001 to 0.002 Gm maximum dose 0.004 Gm, with a maximum per day of 0.002 Gm. Many clinicians, however, have used very much larger doses without ill effects, and the relative activity of certain specimens of the "German" digitalin and other members of the group would seem to indicate that such specimens of "German" digitalin might be given safely in daily doses of a grain, or possibly more.

As "German" digitalin (so called digitalinum purum) is a mixture of very powerful active principles, the proportion of which may vary with changes in the manipulations, it is important that the directions for its preparation should be carefully followed, and caution should be exercised to purchase only such products as the manufacturers can guarantee to have been made with the necessary care.

Preparation—

the latter carefully distilled off, and lead From annealed lead ohol. or as long as it takes up anything. The digitalin purified in this way is dried at a low temperature and finely powdered. (Hager's Handbuch der pharmaceutischen Praxis, edited by B. Fischer and C. Hartwich, ed. 1, Berlin, Julius Springer, 1903, vol. 1, p. 1032)

Tests—

orphous powder soluble in chloroform. It is said to contain digitonin and from 5 to 10% of other glucosides. Sulfate produces with coloration changing to

DIGITALINE NATIVELLE — Digitaline Cristallisee (Nativelle) — A glucosidal substance derived from the dried leaves of *Digitalis purpurea*, first prepared by Nativelle (*J Pharm Chem* 9:225, 1869). The empiric formula of digitaline Nativelle closely approximates $C_{45}H_{84}O_{13}$. It is standardized by the intravenous cat method of Hatcher and Brody so that 0.42 mg equals 1 cat unit, but the therapeutic dose is much less than that of digitalis in terms of cat units.

Actions and Uses — Digitaline Nativelle (digitoxin), the chief active glycoside of *digitalis purpurea* was used by Nativelle in 1868 and first reported in the literature in 1869. It is available in crystalline form, sufficiently pure to be administered by weight. It is almost completely absorbed from the intestinal tract and a given dose produces practically the same therapeutic effect whether given by mouth or by vein. Nausea or vomiting due to local action are almost never encountered. In oral administration the same results are obtained as when administered intravenously. The illustration is administered intravenously, and thus the drug does not need to be administered intravenously.

Dosage — Most patients can be digitalized by the administration of not more than 12 mg, although a few may require a larger amount, while others will show some sign of intoxication from even this quantity. For patients who have received no digitalis in any form for at least two weeks the average dose of 12 mg may advise beginning doses of 0.4 mg with a daily maintenance dose of 0.2 mg may also be accomplished by administering each day a dose of 0.2 mg for a period of one to three weeks even when no larger initial dose has been given.

Tests and Standards —

Digitaline Nativelle appears as thin colorless odorless elongated rectangular plate-like crystals possessing a bitter taste. It is practically insoluble in water, ether and glycerin, soluble in acetone, chloroform, ethyl alcohol and pyridine. Digitaline Nativelle may sinter at 230°C and melts finally at from 253 to 263°C.

Digitaline Nativelle dissolves in cold concentrated hydrochloric acid.

VARICK PHARMACAL CO., INC.

Tablets Digitaline Nativelle: 0.1 mg and 0.2 mg

Solution Digitaline Nativelle: 1 cc Ampuls (0.2 mg) and 2 cc Ampuls (0.4 mg)

DIGITAN—A purified extract of digitalis containing the active principles in the same proportions as they exist in the whole leaf. In digitan, 85 per cent of the inactive substances present in the ordinary extract have been removed and it is free from digitonin. Digitan is physiologically standardized according to the official U S P XII procedure.

Actions and Uses—The same as those of digitalis.

Dosage—The same as that of digitalis.

Preparation—

Digitan is obtained by removing objectionable constituents from an alcoholic extract of digitalis neutralized with alkaline hydroxides by the addition of ether petroleum benzene or some other suitable precipitant, and reducing the purified liquid to a powder by evaporating with milk sugar.

Tests—

Digitan is a greenish yellow odorless bitter powder. The active constituents of digitan are insoluble in cold water and diluted acids but are easily soluble in weak alkalis.

Digitan responds to the following identity test. If 0.1 Gm of digitan is underlaid with about 3 cc of glacial acetic acid which contains 1 per cent of a 5 per cent solution of ferric sulfate there appears a red band (*presence of digitatin*) and above this another at first bright green later changing to dark green and finally blue (*presence of digitonin*).

The physiologic activity is determined by the official U S P procedure.

MERC & Co, INC

Digitan Powder.

Digitan (for Parenteral Use) 1 cc ampuls. A sterilized solution of digitan 0.1 Gm per cubic centimeter.

Tablets Digitan 0.1 Gm.

Tincture Digitan Each 1 cc contains digitan, 0.1 Gm.

U S patent 943 578 (Dec 4, 1909 expired) U S trademark 138 484

DIGITOL—Tincture of Digitalis (Fat Free) Mulford—A biologically standardized, fat free tincture of digitalis corresponding in drug strength to tincture of digitalis U S P and containing 73 per cent alcohol.

Actions and Uses—The same as those of digitalis. Digitol was introduced at a time when the 'fat' of digitalis was believed to cause gastric disturbances. At present the claim of superiority on this basis is not tenable. The only advantage of the defatting process is to make possible a nearly clear mixture of the product with water.

Dosage—From 0.3 to 1 cc.

Preparation.—

Digitalis which has previously been subjected to percolation with petroleum benzine is extracted by percolation with hydroalcoholic menstruum in the usual way.

Digitalol is a brownish green liquid having a characteristic and highly alcoholic odor and a bitter taste. Each cc represents one U S P Digitalis Unit.

SHARP & DOHME, INC

Digitalol (Liquid)

GITALIN (AMORPHOUS).—A glucosidal constituent of *Digitalis purpurea* Linné prepared according to the method of Kraft. It is standardized by the intravenous cat method of Hatcher and Brody (*Am J Pharm* 82:360, 1910) and its potency adjusted to an M L D of approximately 0.75 mg per kilogram of body weight.

Actions and Uses.—The same as those of digitalis.

Dosage.—Full digitalis effects are usually obtained after a total dosage of 4 to 6.5 mg, or from five to eight tablets. These effects may be obtained by the administration of two to three tablets per day for three or four days. The same precautions should be taken with gitalin as with any digitalis preparation or digitaloid drug. Should toxic symptoms, such as nausea or vomiting, occur during the course of digitalization, administration of the drug should be discontinued. After the desired clinical effects have been induced, the patient may be placed on a maintenance dose of 0.25 mg to 0.75 mg (one third to one tablet) daily. The amount varies according to the individual requirements of the patient. Gitalin (amorphous) is less cumulative than digitoxin but more so than ouabain and most tinctures of digitalis. While the biologic cat unit has been determined to be 0.75 mg per kilogram of body weight, gitalin (amorphous) gives good clinical results in amounts ranging from one-third to one half the digitalis equivalent calculated on this basis.

Preparation.—

Dried and ground leaves of *Digitalis purpurea* Linné are extracted with cold, distilled water. This aqueous infusion is then treated with basic lead acetate and the lead subsequently removed by precipitation with sodium sulfate. The resulting filtrate is agitated with chloroform and allowed to separate. From the chloroform extract the gitalin (amorphous) substance is precipitated by means of petroleum ether. The precipitate is subjected to further purification and finally dried in vacuo. The entire process of extraction and purification is conducted without the aid of heat.

Tests.—

Gitalin (amorphous) is a white or slightly buff colored amorphous powder which is readily soluble in chloroform, ether, acetone and alcohol and is slowly soluble in 600 parts of cold water. It is insoluble in petroleum ether and carbon disulfide. Its aqueous solution is neutral to litmus and possesses an intensely bitter taste. It has no sharp melting point but undergoes some decomposition when heated to 110 C and

becomes fluid as the temperature is raised to 150 C. When its aqueous solution is boiled gitalin (amorphous) is converted into anhydrogitalin with a subsequent loss of about 30 per cent in potency.

Dissolve 10 mg of gitalin (amorphous) in 3 cc of glacial acetic acid in a narrow test tube, and add to this one drop of 5 per cent ferric chloride solution. Underlay this solution with concentrated sulfuric acid; a brownish red zone appears at the point of contact. The upper acetic acid layer assumes a bluish green color, gradually changing to indigo blue. Repeat the test without the addition of ferric chloride; a brown zone appears at the point of contact, and the upper acetic acid layer remains green. Concentrated sulfuric acid containing 10 mg of gitalin (amorphous) and a trace of ferric chloride produces a brown color, gradually changing to red and finally to violet. When an aqueous solution of gitalin (amorphous) is heated for one hour at 100 C. its potency is reduced 30 per cent. This 'titer-drop' is a characteristic feature of gitalin (amorphous) and is due to the conversion of gitalin into anhydrogitalin. It does not occur with digitoxin.

RARE CHEMICALS, INC.

Tablets Gitalin (Amorphous), 0.75 mg. Each tablet is scored into segments of 0.25 mg. for convenience in regulation of the daily maintenance dose.

Related Digitalis Principles

OUABAIN—G Strophanthin—'A glycoside occurring in *Acokanthera Ouabain* Arnaud and obtained from the seeds of *Strophanthus gratus* (Wall et Hook.) Baillon (Fam. Apocynaceae)," U. S. P.

For description and standards see the U. S. Pharmacopeia under Ouabain and Ouabain Injection.

Actions and Uses—The pharmacologic action of ouabain is probably qualitatively identical with that of the official strophanthus or strophanthin but ouabain is more active than the official strophanthin when injected intramuscularly or intravenously. This action develops more rapidly, the drug is more quickly excreted and shows less tendency to cumulative action than does digitalis.

Ouabain is used only for injection in place of strophanthus or strophanthin as a substitute for digitalis.

Dosage—Ouabain is absorbed so slowly and so irregularly from the alimentary canal that the oral administration of the drug is not to be recommended and is even considered unsafe.

For intravenous or intramuscular administration the dose is 0.5 mg. and this dose should not be repeated as a rule within less than twenty-four hours. It is best employed dissolved in from 4,000 to 8,000 parts of isotonic solution of sodium chloride. When the intramuscular or intravenous dose is to be repeated within less than twenty-four hours a smaller amount should be administered.

Since ouabain solution may deteriorate rapidly, when sterilized in glass which yields traces of alkali, only solutions which have been kept in alkali-free glass containers should be used.

MERCK & CO., INC.

Ouabain (G-Strophanthin) powder

CARROLL DUNHAM SMITH PHARMACEUTICAL COMPANY

Ouabain Injection Ampuls 0.1 mg in $\frac{1}{2}$ cc and 0.5 mg in 2 cc

Ouabain and Digitalis Tablets Packages containing two 2 cc, 0.5 mg ampuls of ouabain and one vial of 20 tablets digitalis 0.1 Gm

SCILLAREN-B—Glucosidum e Scilla Solubile—The amorphous component of the natural mixture of the glycosides occurring in squill, *Urginea maritima*. Completely dried scillaren B contains approximately 99.5 per cent active glycosidal substance. Scillaren B dried in a high vacuum at 78°C for fifteen hours loses not more than 5 per cent of its weight.

Actions and Uses—The same as those of scillaren.

Dosage—Scillaren B is for intravenous administration when immediate action is indicated. Not more than 0.5 mg of scillaren B should be injected intravenously within twenty-four hours.

Tests and Standards—

Scillaren B occurs as a fine white or slightly yellowish white odorless granular powder possessing a very bitter taste. freely soluble in water, ethyl and methyl alcohol 1 in 5 respectively, very slightly soluble in chloroform 1 in 10,000 and practically insoluble in ether. An aqueous solution is neutral toward litmus. An alcoholic solution of scillaren B is dextrorotatory.

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responds to
uces alkaline

cupric tartrate solution

Dissolve about 0.025 Gm of scillaren B in 1 cc of carbon dioxide

tion at 20°C the specific rotatory power in alcohol $[\alpha]_D^{20}$ falls between +35 and +41.

Ignite about 0.1 Gm of scillaren B accurately weighed; the residue does not exceed 0.1 per cent. Dry about 0.2 Gm accurately weighed

over sulfuric acid in a partially exhausted desiccator for forty eight hours at 20 C the loss in weight does not exceed 2 per cent

Transfer about 0.2 Gm of scillaren B, accurately weighed previously dried over sulfuric acid in a partial vacuum to a 250 cc Erlenmeyer flask, dissolve in 5 cc of water and add 20 cc of a 5 per cent sulfuric acid, heat on a steam bath for six hours, cool, and collect the separated yellowish brown lumps on a Gooch crucible, wash free from acid with water, dry for twenty four hours at 60 C, and weigh the amount of aglucone found is not less than 50 per cent nor more than 57.5 per cent

SANDOZ CHEMICAL WORKS, INC

Solution Scillaren-B: 0.5 mg in 1 cc ampuls

U S patent 1,516,552 (Nov 25 1924 expired) and 1,579,335 (April 6, 1926, expired) U S trademark 173,046

SCILLAREN—*Glucosidum e Scilla Totum*—A mixture of the natural glycosides, scillaren A and scillaren-B, occurring in fresh squill *Urginea maritima*, in the proportions in which they exist in the fresh crude drug, namely, about 2 parts of scillaren-A to 1 part of scillaren B. Completely dried scillaren contains approximately 98 per cent of the active glycosides. Scillaren dried in a high vacuum at 78 C for fifteen hours loses not more than 6 per cent of its weight.

Actions and Uses—The cardiac action of scillaren is essentially similar to that of digitalis, but this action is apparently less persistent than that of digitalis.

Dosage—16 mg orally from three to four times daily until compensation is established or until minor toxic symptoms are induced. After compensation is established, 0.8 mg may be administered from two to four times daily.

Tests and Standards—

Scillaren powder, po 1 in 5, in practically is neutral levorotatory

Dissolve about 0.001 Gm of scillaren in 0.1 cc of methyl alcohol, add 3 cc. of acetic anhydride, followed by the addition of 0.1 cc of sulfuric acid, agitate and cool a violet red color results immediately turning to a bluish green (this color reaction is due to the mixture of scillaren A and B). Dissolve about 0.1 Gm in 10 cc of methyl alcohol add 1 and heat the mixture under five minutes the aglucone, heating for thirty minutes filter, wash with water and dry at 105 C. its melting point is not definite occurring with decomposition. The color reaction character further heating the filtrate

separate by filtration on cooling solidify with tenth normal consisting of a mixture of A and B is removed by filtration the filtrate contains only scillaren B and cleaved sugar but is entirely free from scillaren A

Boil about 2 cc of the filtrate with 5 cc of alkaline cupric tartrate solution; a reduction of the latter results. Transfer the remainder

Dissolve about 0.025 Gm of scillaren in 2 cc of methyl alcohol; a clear colorless solution results, and remains clear on dilution with an equal volume of carbon dioxide-free water (*aglucone*). Add to the foregoing solution 1 cc of lead acetate solution and heat to boiling; results in ten minutes (tannoid substances) of methyl alcohol; a clear colorless solution results. Transfer the remainder

Dissolve about 0.5 Gm of scillaren, accurately weighed, in 25 cc of 75 per cent (by weight) of ethyl alcohol; observe the angular rotation at 20°C; the specific rotary power in alcohol $[\alpha]_{20/D}$ falls between -25 and -35.

Ignite about 0.1 Gm of scillaren, accurately weighed; the residue does not exceed 0.25 per cent. Dry about 0.2 Gm, accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty-eight hours at 20°C; the loss in weight does not exceed 4 per cent.

Transfer about 0.2 Gm of scillaren, accurately weighed, previously dried over sulfuric acid in a partial vacuum to a 250 cc Erlenmeyer flask, dissolve in 5 cc of water and add 20 cc of 5 per cent sulfuric acid, heat on a steam bath for six hours, cool and collect the separated crystalline and oily resinous mixture on a Gooch crucible, and wash free from acid with water, dry for twenty-four hours at 60°C, and weigh; the amount of aglucone found is not less than 48 per cent nor more than 53 per cent.

Scillaren A, a component of scillaren, responds to the following tests for identity and purity.

Scillaren A occurs as a white powder, with a very slight odor. It is soluble in methyl alcohol, alcohol and 1 part in chloroform and gives a neutral reaction. $[\alpha]_{20/D}$ of undried material.

Dissolve about 0.001 Gm. of scillaren A in 0.1 cc of methyl alcohol, and add 3 cc of acetic anhydride, followed by the addition of 0.1 cc

equal volume of carbon dioxide-free water (*aglucone*). Add to the foregoing solution 0.1 cc of lead acetate solution; no immediate coloration or precipitation results (appreciable amounts of tannoid substances). Dissolve about 0.025 Gm. in a mixture of 2 cc of methyl alcohol and 2 cc of water; add 0.5 cc of alkaline cupric tartrate solution and heat to boiling; the blue color persists for some time (reducing free sugars).

Dissolve about 0.5 Gm of scillaren A, accurately weighed in 25 cc of 75 per cent (by weight) of ethyl alcohol, observe the angular rotation at 20 C the specific rotatory power in alcohol $[\alpha]_{20/D}$ falls between -72 and -78

Incinerate about 0.1 Gm of scillaren A, accurately weighed the residue does not exceed 0.1 per cent Dry about 0.2 Gm, accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty eight hours at 20 C the loss in weight does not exceed 2.5 per cent

Transfer about 0.2 Gm of scillaren A, accurately weighed previously dried over sulfuric acid in a partial vacuum to a 250 cc Erlenmeyer flask, add 10 cc of methyl alcohol and 10 cc of tenth normal sulfuric acid solution reflux on a steam bath for fifteen minutes disconnect the condenser and boil on the steam bath until reduced to about a 10 cc volume, cool and collect the crystals formed on a Gooch crucible wash free from acid with water and dry to constant weight at 105 C the amount of aglucone found should not be less than 48 per cent, nor more than 53 per cent

SANDOZ CHEMICAL WORKS, INC.

Tablets Scillaren: 0.8 mg

Solution Scillaren: Each cubic centimeter represents 0.8 mg of scillaren

U S patent No 1 516 552 (Nov 25, 1924, expired) and No 1 579 338 (April 6, 1926, expired) U S trademark 173 046

Dosage—2 cc (40 drops) three to four times daily after compensation is established 1 cc (20 drops) two to four times daily A dropping device is supplied with each package designed to yield 20 drops per cubic centimeter

URGININ—A mixture of two water insoluble glycosides, urginin A and urginin B, derived from squill, in the proportions in which they exist in the drug, namely, about equal parts The product is standardized so that the variation in the proportion of each glycoside is not more than plus or minus 2.5 per cent (from 50 per cent), i e., 47.5 to 52.5 per cent Urganin dried in a high vacuum at 50 C for five hours loses not more than 2 per cent of its weight Physiological standardization by the Hatcher Brody cat method as modified by C DeLind Van Wijngaarden, Arch exper Path u Pharm, 113 40, 59, 114 21, 1926 and by J H Burn, Methods of Biological Assay, Oxford University Press, 1928 demonstrates the lethal dose of urginin for cats to be 0.2 mg per Kg (one cat unit)

Actions and Uses—The cardiac action of urginin is essentially similar to that of digitalis

Dosage—Where digitalis or other cardioactive glycosides have not been used within one week and where prompt and full therapeutic effects are desired, the total dose of urginin is estimated at the rate of 1 mg of urginin per ten pounds of body weight, approximately one half of the calculated amount is given as the initial dose followed in six hours by one fourth of the

total dose and then at intervals of six hours one half of the immediately preceding dose until the full effects of the drug are observed

Tests and Standards—

Urginin occurs as a pale yellow, granular powder possessing a slight characteristic odor and an extremely bitter taste soluble in acetone alcohol ethyl acetate glacial acetic acid dilute alkali carbonate and hydroxide solutions sparingly soluble in chloroform, practically insoluble in water, carbon tetrachloride ether and purified petroleum benzene. A saturated aqueous solution is neutral to litmus. An alcoholic solution is levorotatory. Dissolve about 0.001 Gm of urginin in 2 cc of acetic anhydride followed by the addition of

sugars)

Ignite about 0.1 Gm of urginin, accurately weighed the residue does not exceed 0.25 per cent. Dry about 0.2 Gm of urginin accurately weighed over sulfuric acid in a partially exhausted desiccator for forty eight hours at 20 C the loss in weight does not exceed 4 per cent. Dissolve about 0.5 Gm of urginin accurately weighed in 25 cc of 95 per cent ethyl alcohol observe the angular rotation at 20 C the specific rotatory power $[\alpha]_{20/D}$ falls between -18.0 and -21.5 . Transfer about 0.5 Gm of urginin, accurately weighed previously dried over sulfuric acid in a partial vacuum to a suitable Erlenmeyer flask dissolve in 7 cc of alcohol followed by the addition of 7 cc of a mixture of 1 cc of sulfuric acid and 25 cc of water connect with condenser and reflux on a steam bath for six hours disconnect the condenser, neutralize the mixture with normal sodium hydroxide solution using phenolphthalein as an indicator add 0.1 cc of sulfuric acid remove the alcohol by heating on the steam bath until reduced to about a 10 cc volume add 10 cc of water mix thoroughly and evaporate to about 10 cc cool and collect the separated crystalline and dark waxy resinous residue on a filter paper wash

LEDERLE LABORATORIES INC

Tablets Urginin 10 mg (coated and plain)

U S patent 1 972 876 (Sept 11 1934 expires 1951) U S trade mark 324 695

STROPHANTHIN—"A glycoside or a mixture of glycosides obtained from *Strophanthus Kombe* Oliver (Fam *Apo cynaceae*)—U S P

"Strophanthin, when assayed as directed, shall possess a potency per mg equivalent to 0.5 mg of U S P Ouabain Reference Standard 'U S P

For description and standards see the U S Pharmacopeia under Strophanthin

Organic Nitrates

The esters of nitric acid and the higher alcohols (glycerin, propanetriol, erythrite, butanetetrol, etc.) have an action on the blood vessels similar to that of the inorganic nitrites (sodium nitrite) and that of the nitrous acid esters of the alcohols (amyl nitrite, ethyl nitrite). This is generally attributed to the formation in the body of nitrites from them.

ERYTHRITYL TETRANITRATE TABLETS—Erythrol Tetranitrate Tablets—Tetranitrol Tablets—"Contain not less than 93 per cent and not more than 107 per cent of the labeled amount of erythrityl tetranitrate [$C_6H_8(NO_3)_4$]" U S P

For description and standards see the U S Pharmacopeia under Erythrityl Tetranitrate Tablets

Actions and Uses—Erythrityl tetranitrate is a vasodilator like nitroglycerin. Its action is slower and more lasting, beginning in fifteen minutes and persisting for three or four hours.

It is said to be useful in angina pectoris and certain vascular diseases. It is reported as especially useful as a prophylactic in preventing anginal pain. Its use is sometimes attended with severe headache.

Dosage—From 30 mg to 60 mg every four to six hours.

BURROUGHS WELLCOME & Co, INC

Tabloid Erythrityl Tetranitrate 16 mg, 32 mg and 65 mg

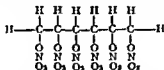
MERCK & Co, INC

Tablets Erythrol Tetranitrate 16 mg and 32 mg

Organic Nitrates

MANNITOL HEXANITRATE—Mannitol Nitrate—Nitromannite— $C_6H_8O_6N_6$ M W 452.17—An explosive compound formed by the nitration of mannitol a sugar alcohol. Its

stability at ordinary temperatures is such that it may be used commercially but it is distinctly less stable than nitroglycerin at 75 C. Its use for pharmaceutical preparations is only in admixture with carbohydrate substances in dilutions corresponding to 1 part of mannitol hexanitrate to 9 or more parts of carbohydrate. In such dilutions mannitol hexanitrate is non-explosive. Mannitol hexanitrate has the following structural formula



Actions and Uses—Mannitol hexanitrate exerts the vasodilator action of the nitrite ion (NO_2), causing a relatively persistent relaxation of smooth muscle especially that of the smaller blood vessels. This relaxation causes a fall in blood pressure occurring within fifteen to thirty minutes and lasting four to six hours. It also relaxes the coronary vessels and frequently provides relief from the pain of angina pectoris although too frequent dosage may cause such a fall in blood pressure that the blood flow continues to be inadequate in spite of the vasodilatation. It has no direct effect on the myocardium.

Toxic effects include the formation of methemoglobin (which should constitute a warning concerning the use of nitrites by anemic persons), rise in intraocular tension, headache, increase

Dosage—Mannitol hexanitrate may be administered in 15 to 60 mg doses at intervals of four to six hours. Occasionally this dose may be exceeded but careful watch of the blood pressure and the patient should be kept at all times so that the development of undesirable side effects and the patient's tolerance may be noted. The dosage should be kept at a minimum compatible with satisfactory results. Patients with extensive arteriosclerosis may not present reductions in blood pressure and as in other instances, if no reduction occurs medication with mannitol hexanitrate should be discontinued.

Tests and Standards—

Mannitol hexanitrate tablets are partially soluble in alcohol and in
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 glass

screen while determining the melting point) It is insoluble in water and soluble in alcohol and in ether It may be recrystallized from hot alcohol in the form of characteristic long needles in regular clusters

Transfer an accurately weighed portion of powdered tablets, containing about 0.25 Gm of mannitol hexanitrate to a glass stoppered Erlenmeyer flask and extract the powder with 25 cc of ether, decant the extract through a dry filter paper into a tared dish and repeat the extraction five times, evaporate the combined filtrates to 3 cc. at a temperature not exceeding 35 C and allow the remaining solution to evaporate spontaneously Dry the residue over calcium chloride in a vacuum desiccator for eight hours and weigh the mannitol hexanitrate the amount of mannitol hexanitrate found corresponds to not less than 93 per cent nor more than 107 per cent of the labeled amount

ABBOTT LABORATORIES

Tablets Mannitol Nitrate. 16 mg and 32 mg Each tablet contains not less than 93 nor more than 107 per cent of the labeled amount of mannitol hexanitrate and also contains at least 9 parts of carbohydrate by weight

Quinidine

QUINIDINE — *Quinidina* — An alkaloid, $C_{20}H_{24}O_2N_2 + 2H_2O$, obtained from the bark of various species of *Cinchona*

Quinidine is obtained from cinchona bark as a by product in the manufacture of quinine, to which it is closely related, being its stereoisomer

Actions and Uses—*Quinidine*, like quinine, is a protoplasmic poison It affects protozoa more than bacteria but less powerfully than quinine At one time it was used, to some extent, as a substitute for quinine because it was then much the cheaper preparation It has the antimalarial action of quinine, and may be tolerated by some patients who have an idiosyncrasy to quinine

Quinidine acts upon the heart in such manner as to bring about cessation of fibrillation of the auricles in a certain proportion of instances *Quinidine* and other cinchona alkaloids are the only drugs known to have this specific effect The pharmacology of the drug has been extensively investigated It has been shown that quinidine increases the refractory period of the auricular muscle and decreases its irritability and the rate of conductivity Its chief action is upon the cardiac muscle In ordinary doses the heart is slowed and the auriculo ventricular conduction time is lengthened *Quinidine* is used to restore the normal rhythm of the heart in cases of auricular fibrillation This has been brought about in approximately 50 per cent of the reported cases in which the drug has been used It is apparently most efficacious in the cases of fibrillation of short duration or of the paroxysmal type It may also stop fibrillation of several years duration It is least effective in cases of fibrillation with marked cardiac insufficiency It is useful in slowing the rate in ventricular tachycardia fol

lowing infarction of the myocardium. Quinidine is not without some unpleasant and even dangerous effects. Some patients appear much more susceptible to its intoxication than others. The untoward symptoms brought about by its use in these patients are nausea, vomiting, convulsions, palpitation, headache, faintness and flushing. In most cases following the administration of the drug, the pulse increases in rapidity before the normal rhythm is established. In some cases the effect of the drug is restricted to this alteration of rhythm. In a few instances such serious results as rapid idioventricular rhythms (ventricular tachycardia) have been initiated during the course of therapy. Toxic effects may appear after the establishment of a normal rhythm. Some cases have been reported in which sudden death occurred a short time after the drug had been stopped. The drug is rapidly eliminated and it apparently has no cumulative effect.

Dosage—Quinidine is generally administered as quinidine sulfate. Commonly 0.2 Gm of quinidine sulfate is given as a preliminary dose and is repeated after two hours to determine the patient's susceptibility to the drug. If there are no symptoms following this preliminary dose, therapeutic administration is begun on the following day when from 0.2 Gm to 0.4 Gm is given from three to five times daily, for one to three days. As a rule if the establishment of the normal rhythm can be effected the change occurs after from one to three days treatment. The maximum dose per day advised by most authors is from 1 to 2 Gm. In ventricular tachycardia following cardiac infarction larger doses are sometimes required and are well tolerated. If toxic symptoms occur, the administration of the drug should be discontinued. Intravenous administration is dangerous and is not recommended.

Tests and Standards—

benzine

The saturated aqueous solution of quinidine is alkaline to litmus and its alcoholic solution is dextrorotatory. A solution of quinidine in diluted sulfuric acid (1 in 1000) shows a strong blue fluorescence.

Quinidine loses its water of hydration at 100 C. The dried alkaloid melts at about 168 C.

potassium iodide solution and agitate an orange yellow, crystalline precipitate forms after an interval (*distinction from quinine*)

Dissolve 0.5 Gm of quinidine in 15 cc of boiling distilled water with just enough sulfuric acid to form a solution neutral to litmus paper, and add 5 cc of potassium iodide solution. Agitate the mixture gently, cool it to 15 C, and keep it at this temperature for one hour, with occasional stirring a white precipitate is formed (*difference from quinine*). Filter out the precipitate and add 2 drops of ammonia water to the filtrate not more than a slight turbidity results (*limit of other cinchona alkaloids*). Care must be taken to have the liquid perfectly neutral after the addition of the potassium iodide solution, if slightly acid very dilute ammonia water must be added drop by drop with constant stirring until exact neutrality to litmus is attained.

A solution of about 0.1 Gm of quinidine in 5 cc of sulfuric acid is not darker than pale yellow (*organic impurities*).

Incinerate about 1 Gm of quinidine accurately weighed the ash does not exceed 0.1 per cent.

Dry about 1 Gm of quinidine accurately weighed to constant weight at 100 C the loss does not exceed 11 per cent.

MALLINCKRODT CHEMICAL WORKS

Quinidine (Powder)• bulk

MERCK & Co, INC

Quinidine (Powder) bulk

QUINIDINE SULFATE — "A sulfate of an alkaloid obtained from the bark of the stem or of the root of various species of cinchona and their hybrids (Fam *Rubiaceae*)"
U S P

For description and standards see the U S Pharmacopeia under Quinidine Sulfate and Quinidine Sulfate Tablets

Actions and Uses—See preceding article, Quinidine

Dosage—See preceding article Quinidine Quinidine sulfate may be administered in the form of cachets capsules pills or tablets

ABBOTT LABORATORIES

Capsules Quinidine Sulfate 0.2 Gm

DAVIES, ROSE & COMPANY, LTD

Tablets Quinidine Sulfate• 0.2 Gm

MALLINCKRODT CHEMICAL WORKS

Quinidine Sulfate (Powder) bulk

MERCK & Co, INC

Quinidine Sulfate (Powder) bulk

sugar shows no more sulfate than corresponds to 0.3 cc of fiftieth normal sulfuric acid according to the U S P X test. A solution equivalent to 5 Gm of invert sugar evaporated to dryness and ashed yields a residue weighing not more than 0.004 Gm. A solution equivalent to 5 Gm of invert sugar yields not more ammonia than is equivalent to 0.5 cc of hundredth normal hydrochloric acid. A solution containing 16 per cent of invert sugar calculated from its copper reducing power, when examined by means of the polariscope has a specific rotation of $[\alpha]_D^{25}$ between -16 and -18.5 .

Dilute exactly 10 cc of the original to exactly 500 cc, transfer 10 cc of this solution to a 250 cc beaker and assay for invert sugar according to paragraphs 37 and 38 on page 49 of the 1936 edition of the A O A C Manual; the amount of invert sugar is within 5 per cent of the amount claimed. Transfer 50 cc of the prepared solution to a 100 cc standard flask, invert according to paragraph 23 C page 473 of the A O A C Manual and assay for sucrose according to paragraph 28 page 476 of the A O A C Manual, the weight of sucrose is not greater than 4 per cent of the weight of invert sugar found.

SODIUM MORRHUATE—A mixture of the sodium salts of the saturated and unsaturated fatty acids occurring in cod liver oil.

Actions and Uses—The action of sodium morrhuate is that of a sclerosing agent. It is employed in solution with addition of a local anesthetic for the obliteration of varicose veins. Solutions in concentrations of more than 5 per cent are not recommended and the possibility of sensitization or idiosyncrasy to sodium morrhuate should be kept in mind to avoid reactions which have been reported in susceptible individuals.

Dosage—One half to 1 cc of a 5 per cent solution is a relatively safe preliminary test dose and its effects should be studied for 24 hours before proceeding with further injections. An average of 1 cc is the amount injected at any one site and should not exceed 2 cc. The number of injections made in one day varies with the patient and should not comprise a total amount of more than 5 cc. To guard against the development of sensitivity it is recommended that the interval of time between the first two injections be not more than five days.

Tests and Standards—

Sodium morrhuate is a pale yellowish granular powder possessing a slight fishy odor. It is soluble in water.

Incinerate about 1 Gm of sodium morrhuate; the residue responds to test for sodium carbonate. Dissolve about 0.01 Gm of sodium morrhuate in 10 cc of water, add 1 cc of chloroform followed by one drop of sulfuric acid and shake; a violet red color results gradually changing to a reddish brown.

Dry about 1 Gm of sodium morrhuate accurately weighed at 100°C

not less than 7 per cent nor more than 7.8 per cent water loss to the dried substance

ENDO PRODUCTS, INC

Solution Sodium Morrhuate 5% with Benzyl Alcohol
 2% 2 cc and 5 cc ampuls and 25 cc bottle Each cubic centimeter contains sodium morrhuate 50 mg and benzyl alcohol 20 mg in aqueous solution

NATIONAL DRUG COMPANY

Solution Sodium Morrhuate with Quinine 5 cc ampuls and 25 cc ampul vials Each cubic centimeter contains sodium morrhuate 50 mg quinine alkaloid 20 mg and benzyl alcohol 0.2 Gm in aqueous solution

U. S. patent 2,037,196 (April 14, 1936 exp. res. 1953) and 2,046,116 (June 30, 1936 exp. res. 1953)

Solution Sodium Morrhuate 5% with Benzyl Alcohol
 2% 5 cc ampuls and 25 cc ampul vials Each cubic centimeter contains 50 mg sodium morrhuate and 20 mg benzyl alcohol in aqueous solution

G. D. SEARLE & CO

Solution Sodium Morrhuate 5% with Benzyl Alcohol
 2% 5 cc and 60 cc (serum type ampuls) Each cubic centimeter contains 50 mg sodium morrhuate and benzyl alcohol 20 mg in aqueous solution

ULMER PHARMACAL COMPANY

Sodium Morrhuate 5% Solution with Benzyl Alcohol
 3% 5 cc and 20 cc vials Each cubic centimeter contains sodium morrhuate 50 mg benzyl alcohol 30 mg and phenol 5 mg in aqueous solution

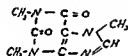
THE UPJOHN COMPANY

Solution Sodium Morrhuate 5% with Benzyl Alcohol
 2% 2 cc ampuls and 30 cc vials Each cubic centimeter contains sodium morrhuate 50 mg and benzyl alcohol 20 mg in aqueous solution

CHAPTER X

CENTRAL NERVOUS SYSTEM STIMULANTS

CAFFEINE and SODIUM BENZOATE—"A mixture of caffeine and sodium benzoate, containing, when dried to constant weight at 80° C., not less than 47 per cent and not more than 50 per cent of anhydrous caffeine ($C_8H_{10}N_4O_2$) and not less than 50 per cent and not more than 53 per cent of sodium benzoate ($NaC_7H_5O_2$)." *U S P*



For description and standards see the *U S Pharmacopeia* under Caffeine and Sodium Benzoate and Caffeine and Sodium Benzoate Injection

CARBON DIOXIDE—Carbonic Acid Gas—"Contains not less than 99 per cent by volume of CO_2 ." *U S P*

For description and standards see the *U S Pharmacopeia* under Carbon Dioxide

Actions and Uses.—Carbon dioxide is the natural stimulant to respiration. It is frequently added to oxygen in varying proportions for supplying artificial respiration, and as a stimulant to the respiratory center. The proportions must be regulated carefully. A great excess of carbon dioxide causes death by asphyxia.

OXYGEN—"Oxygen contains not less than 99 per cent by volume of O_2 ." *U S P*

For description and standards see the *U S Pharmacopeia* under Oxygen

Caution. The usual precautions concerning use of oxygen apparatus must be followed. Special precaution must be observed against use of oil on valves.

Actions and Uses.—Oxygen is administered for the purpose of relieving difficult respiration in cases of mechanical hindrance
 " the treatment of carbon
 " th nitrogen monoxide
 " oxygen containing from
 " for resuscitation

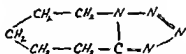
OXYGEN-CARBON DIOXIDE MIXTURE—A mixture in various proportions of carbon dioxide and oxygen

For description and standards see the U S Pharmacopeia under Carbon Dioxide and Oxygen respectively

Caution The usual precautions concerning use of oxygen apparatus must be followed Special precaution must be observed against use of oil on valves

Actions and Uses—Oxygen carbon dioxide mixture in varying proportions for supplying artificial respiration and as a stimulant to the respiratory center

METRAZOL.—Pentamethylenetetrazol—



Actions and Uses—The action of metrazol resembles that of camphor but it is claimed to be more dependable mainly on account of its greater solubility in water Its action following injection intravenously or subcutaneously is induced promptly Metrazol stimulates the vasomotor and respiratory centers in experiments on normal animals but an experienced worker in this field found it a very uncertain respiratory stimulant in conditions of depressed respiration in animals in which carbon dioxide epinephrine and ephedrine were markedly effective that as a circulatory stimulant it usually caused a rise of blood pressure only in convulsive doses that it did make irregularly beating hearts beat more regularly but only at expense of depression of rate and amplitude The use of metrazol is reported as a sustaining agent and restorative in chronic cardiac and circulatory insufficiency in pneumonia and in other infectious diseases It has been reported to be of value in emergencies due to cardiovascular collapse in shock in respiratory failure and in narcotic depression On the other hand it sometimes causes capillary dilatation in the splanchnic region and animal experiments indicate that the intravenous injection may be distinctly dangerous It may be combined with digitalis and the xanthine diuretics

Metrazol has come into extensive use in the treatment of mental disorders in doses which induce convulsions Reports have appeared of minor fractures of the vertebrae without paralysis induced by these convulsions hence this convulsive treatment should be instituted only by psychiatrists or in an institution where the necessary care can be given

Dosage—Intramuscularly subcutaneously or intravenously from 0.1 to 0.3 Gm repeated as required orally from 0.1 to 0.3 Gm several times daily

Tests and Standards—

Metrazol occurs as biaxial optically negative white crystals that are freely soluble in water. It melts at 57.58°C.

tion

Transfer about 0.2 Gm. of metrazol accurately weighed to a wide mouth weighing bottle, allow to stand over calcium chloride; the loss in weight is not more than 0.1 per cent.

Transfer about 0.2 Gm. of metrazol accurately weighed to a platinum dish and incinerate; the ash is not weighable.

Determine nitrogen by the Dumas method as described in Clarke's Handbook of Organic Analysis, ed. 2, New York: Longmans Green & Co., 1916, p. 199; the nitrogen is not less than 40.4 nor more than 40.9 per cent.

BILHUBER KNOLL CORP.

Solution Metrazol 1 cc and 3 cc ampuls. Each 1 cc contains 0.1 Gm. of metrazol in aqueous solution with 0.1 per cent sodium phosphate.

Metrazol Oral Solution 10 per Cent. An aqueous solution containing metrazol, 0.1 Gm. per 1 cc.

Metrazol Sterile Aqueous Solution 10 per Cent. A sterile solution containing metrazol 0.1 Gm. per cubic centimeter, for parenteral administration.

Tablets Metrazol 0.1 Gm.

U. S. patent 1,599,493 (Sept. 14, 1926, expired). U. S. trademark 249,687.

idine 3(β)-carbox-
ethylamide—The
nicotinamide—

Actions and Uses—Experiments involving several species of animals indicate that the action of nikethamide is mainly on the central nervous system. In animals the drug appears to stimulate medullary centers giving rise to an increased rate and depth of respiration and to peripheral vasoconstriction. Possibly the vasoconstriction may be in part due to a peripheral action.

It has been suggested that the use of nikethamide as an agent to raise blood pressure in human beings, but the results are not consistent; it has been suggested that any rise in blood pressure may be secondary to improved respiration and to stimulation of the reflex centers. Small doses in experimental animals exert no action on the coronary vessels, but larger doses may increase the coronary flow. However, clinical evidence for the use of nikethamide to promote increased coronary blood flow is not conclusive.

Dissolve about 30 Gm of nikethamide in 10 cc of 10 per cent aqueous solution of sodium hydroxide. The solution is clear, nearly colorless and free from the odor of pyridine. It yields only a faint yellow color on the addition of 0.5 cc of 10 per cent aqueous solution of ferric chloride.

The solution becomes only faintly opalescent on the addition of 0.5 cc of 10 per cent aqueous solution of sodium hydroxide. The solution yields a faint yellow color on the addition of 0.5 cc of 10 per cent aqueous solution of ferric chloride.

The solution becomes only faintly opalescent on the addition of 0.5 cc of 10 per cent aqueous solution of sodium hydroxide. The solution yields a faint yellow color on the addition of 0.5 cc of 10 per cent aqueous solution of ferric chloride.

(nicotinic acid)

Warm 10 Gm of nikethamide for one hour with 3 cc of dilute hydrochloric acid and 6 cc of water, cool and add 5 cc of sodium hydroxide solution. The solution yields no distinct yellow color (foreign organic impurities).

A solution made by dissolving 1 Gm of nikethamide in 5 cc of carbon disulfide is clear (water).

Ash 1 Gm of nikethamide. The residue is negligible.

Transfer 25 mg to 50 mg of nikethamide accurately weighed to a 50 cc Kjeldahl digestion flask and add 1 cc of water and 1 cc of con-

ABBOTT LABORATORIES

Sterile Nikethamide 25%, W/V 15 cc ampul

GEORGE A. BREOV & COMPANY, INC.

Solution Nikethamide 25%, W/V 1 cc and 2 cc ampuls and for oral use 15 cc, 88.7 cc and 480 cc bottles

Sterile Solution Nikethamide 25%, W/V 1½ cc ampuls

BUFFINGTON & INC

Sterile Solution Nikethamide 25%, W/V 2 cc and 5 cc. ampuloids

THE DRUG PRODUCTS CO INC

Solution of Nikethamide 25%, W/V 15 cc ampuls 30 cc vials with chlorobutanol 0.5 per cent added as a preservative

ENDO PRODUCTS INC

Solution Nikethamide 25%, W/V 15 and 5 cc ampuls and for oral administration 15 cc vials

FLINT, LATON & COMPANY

Solution Nikethamide 25%, W/V 2 cc and 5 cc. ampuls

LAKEVIEW LABORATORIES INC

Solution of Nikethamide 25%, W/V 15 cc ampuls with 0.5 per cent chlorobutanol added as a preservative 15 cc vials with dropper for oral use 15 cc dial for injection with 0.5 per cent chlorobutanol

CARROLL DUNHAM SMITH PHARMACEUTICAL CO

Solution Nikethamide 25%, W/V 15 cc vials

SMITH DORSEY COMPANY

Solution Nikethamide 25%, W/V 15 cc and 5 cc ampuls

THE UPJOHN COMPANY

Solution Nikethamide 25%, W/V 15 cc and 10 cc ampuls and 887 cc bottles

WM R WARNER & CO INC

Solution Nikethamide 25%, W/V 2 cc and 5 cc ampuls

CHAPTER XI

CHOLERETICS

Bile Salts and Related Compounds

The bile of man and of several animals contains the sodium salts of several conjugated oxycholic acids in varying proportions. In ox and human biles glycocholic acid, $C_{26}H_{46}O_6N$, and taurocholic acid, $C_{26}H_{46}O_7NS$, are prominent constituents. Fresh ox bile is said to contain about 3 per cent each of sodium glycocholate and sodium taurocholate.

Actions and Uses.—The bile salts constitute the main active principles of bile and therefore share the actions and uses of the latter, perhaps with the advantage of more constant composition. When injected into the circulation they cause severe nervous and cardiac depression not observed when they are given by the mouth. They are generally credited with a slight antiseptic and laxative action, with enhancing the efficiency of the resinous hydragogue cathartics, and a prominent role in the digestion and absorption of fat. They stimulate the secretory activity of the liver, increasing both the fluids and solids of the bile.

They have been used with doubtful rationale in obstructive

The sodium glycocholate and taurocholate may be separated in the following manner. Dry ox bile is treated with absolute alcohol and the tincture precipitated by ether in excess. Both salts are deposited and the glycocholate crystallizes on standing; the taurocholate remains in amorphous form, resembling oil or resinous matter. If the deposit is dissolved in water, solution of lead acetate will throw down a lead glycocholate, while the addition of lead subacetate to the remainder will precipitate the taurocholate.

Tests. All the bile acids respond to Pettenkoffer's test. A small portion of the salt is dissolved in a little concentrated sulfuric acid in a small porcelain dish and warmed, care being taken that the temperature does not rise higher than from 60 to 70 C. A 10 per cent solution of cane sugar is then added drop by drop while the liquid is stirred with a glass rod. If compounds of cholic acid are present a beautiful red color will appear which does not disappear at room temperature, but usually in the course of a day becomes bluish violet.

Extracts of Bile

BILE SALTS fresh ox bile,
consisting essentially of . . . sodium tauro-
cholate, in the . . .

Actions and Uses—See preceding general article, Bile Salts and Related Compounds

Dosage—From 10 mg to 0.2 Gm

FAIRCHILD BROS & FOSTER

Bile Salts: bulk

Capsules Bile Salts: 0.2 Gm

GLYCOTAURO—Bile Salts—Concentrated ox bile, freed from bile pigments, containing more than 50 per cent of the natural mixture of sodium glycocholate and sodium taurocholate. Each gram represents approximately 15 cc of fresh ox bile.

Actions and Uses—See preceding general article Bile Salts and Related Compounds

Preparation—

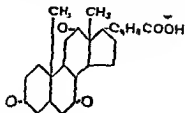
Glycotauro is prepared by evaporating ox bile in the presence of animal charcoal, extracting the residue with purified methyl alcohol filtering, evaporating the filtrate and mixing the residue with glycerin. Glycotauro is a soft semisolid mass of light brown color, bilelike odor and slightly bitter taste. It is easily soluble in water and alcohol. Its specific gravity is about 1.22.

HANSON, WESTCOTT & DUNNING, INC

Capsules Glycotauro 39 mg (half size) and 85 mg

Enteric Coated Tablets Glycotauro* 78 mg coated with salol

DEHYDROCHOLIC ACID—An oxidation product of cholic acid derived from natural bile acids



Actions and Uses—Dehydrocholic acid is useful for its ability to increase the volume of the bile (hydrocholeretic action) it does not stimulate evacuation of the gallbladder (it is not a cholagogue) its effect on the secretion of bile constituents

(choleteretic action) is uncertain. The production of hydrocholeresis may be of value to encourage drainage of the bile ducts by removal of mucus inspissated bile and debris and to discourage the ascent of infection in these structures in cholecystitis, noncalculous cholangitis and other conditions involving biliary stasis not due to complete mechanical obstruction. It should be kept in mind that a copious flow of bile can accomplish a flushing of the ducts but not per se of the gallbladder. The use of dehydrocholic acid in cholecystitis with or without

in cases where
the presence of stasis
decreased output of
eresis may indirectly
induced by the con

less certain in the unoperated patient but may be encouraged by hydrocholeresis in conjunction with an antispasmodic in the presence of spasm of the sphincter of Oddi (spasm of this structure is less readily produced if the liver is secreting freely). Dehydrocholic acid may be employed similarly to encourage maintenance of T tube surgical drainage of an infected common duct and as an aid in the removal of small stones or foreign material overlooked at operation. It is proposed for the purpose of outlining the bile ducts at operation and of accelerating the appearance of the gallbladder shadow and hastening removal of residual tetraiodophenolphthalein from the biliary tract in cholecystography.

Experimental evidence indicates that dehydrocholic acid does not significantly affect the rate of clearance of jaundice following relief of biliary obstruction and confirms the pharmacologic observation that bile salts do not affect the excretion of bile pigments. A few clinical studies favor the use of the drug in the treatment of arsenical and other forms of toxic hepatitis and of hepatic dysfunction and as a diuretic—alone or in combination with the mercurials—in the treatment of ascites due to hepatic congestion in cardiac decompensation, cirrhosis or some other form of liver damage but these have been too poorly controlled to warrant further recognition of such uses until more unequivocal evidence is available.

Dehydrocholic acid acts as a mild diuretic. It has been shown to produce diuresis in edematous patients when this edema is of cardiac origin but it is less effective than the mercurials for this purpose. However as is the case with certain other mild diuretics when given with the mercurials it potentiates their diuretic effect.

Dehydrocholic acid is contraindicated in complete mechanical biliary obstruction because the production of hydrocholeresis in this condition is irrational if not actually harmful. Its use in the presence of severe hepatitis may also be questioned on the

ground that this condition may be aggravated or may reduce the hydrocholeretic effect although more evidence is needed on these points before hepatitis can be regarded as a contraindication to the use of the drug

Dosage—From 0.25 to 0.5 Gm two to three times daily after meals for a period of four to six weeks

Tests and Standards—

Dehydrocholic acid occurs as a fine colorless crystalline powder with a bitter taste sparingly soluble in alcohol and glacial acetic acid. It melts at 233-235 C.

Boil about 1 Gm of dehydrocholic acid with 100 cc of water for two minutes; no odor develops; cool and filter; separate portions of 10 cc each of the filtrate yielding acid and 1 cc of silver nitrate

on saturation with hydrogen

Dry about 1 Gm of dehydrocholic acid accurately weighed at 100 C. The loss in weight does not exceed 1.5 per cent. Incinerate about 1 Gm of dehydrocholic acid accurately weighed; the residue does not exceed 0.1 per cent. Dissolve in 40 cc of previously neutral water and titrate with phenolphthalein as indicator; solution nor more than 101.5 per cent

GEORGE A. BRENN & COMPANY, INC.

Tablets Dehydrocholic Acid 0.25 Gm

BURROUGHS WELLCOME & CO., INC.

Tabloid Dehydrocholic Acid 0.243 Gm

LAKESIDE LABORATORIES, INC.

Tablets Dehydrocholic Acid 0.25 Gm

RIFDEL DE HARN DIVISION OF AMES COMPANY, INC.

Decholin (Powder) bulk Dehydrocholic acid

Tablets Decholin 0.243 Gm

U. S. trademark 315 067

SMITH DORSEY COMPANY

Tabloid Dehydrocholic Acid 0.243 Gm

SODIUM DEHYDROCHOLATE—The sodium salt of dehydrocholic acid

Actions and Uses—The actions and uses of sodium dehydrocholate are the same as those of dehydrocholic acid

After intravenous injection decholin sodium is a mild diuretic. It has been shown to produce diuresis in edematous patients when this edema is of cardiac origin but it is less effective than the mercurials for this purpose. However, as is the case with certain other mild diuretics when given with the mercurials it potentiates their diuretic effect.

Sodium dehydrocholate is also useful in the determination of the arm to tongue circulation time as a diagnostic aid in certain conditions affecting the velocity of the blood flow. It is contraindicated for such use in the presence of bronchial asthma.

Dosage — Sodium dehydrocholate is administered intravenously. One injection is given on each of three successive days. According to the urgency of the case, the first dose consists of from 5 to 10 cc of the 20 per cent solution the second and third of 10 cc.

For determination of the arm to tongue circulation time 3 to 5 cc are rapidly injected (2 to 3 seconds) through an 18 gauge needle into a cubital vein with the subject in the supine position. The time is recorded from the beginning of injection to the perception of a bitter taste (average normal range 9 to 16 seconds).

Tests and Standards—

Sodium Dehydrocholate occurs as a fine colorless crystalline powder with a very bitter taste soluble in water and alcohol. An aqueous solution is alkaline to litmus.

Dissolve about 1 Gm of sodium dehydrocholate in 200 cc of water add an excess of hydrochloric acid collect the resultant dehydrocholic acid on a filter wash and recrystallize from 80 per cent acetic acid it melts at 233-238 C.

Dissolve about 0.5 Gm of sodium dehydrocholate in 100 cc of water acidify with hydrochloric acid and filter. Separate portions of 10 cc each of the filtrate yield no turbidity with 1 cc of barium chloride solution (*sulfate*) no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 1 Gm of sodium dehydrocholate accurately weighed to constant weight at 100 C. The loss in weight does not exceed 7 per cent. Weigh accurately about 1 Gm in a tared platinum crucible add 2 cc of sulfuric acid gently heat while fumes of sulfur trioxide are evolved repeat using two portions of 1 cc of sulfuric acid respectively, ignite cool and weigh as sodium sulfate. The percentage of sodium corresponds to not less than 5.3 per cent nor more than 5.6 per cent when calculated to the dried substance.

GEORGE A. BREON & COMPANY, INC

Solution Sodium Dehydrocholate 20%, W/V 5 cc ampuls

ENDO PRODUCTS, INC

Solution of Sodium Dehydrocholate 20%, W/V 3 cc and 10 cc ampuls

LAKESIDE LABORATORIES, INC

Solution of Sodium Dehydrocholate 20% W/V. 10 cc ampul and 30 cc vial preserved with 0.5 per cent chlorobutanol

RIEDLI DE HAEN DIVISION OF AMES COMPANY, INC

Solution Decholin-Sodium, 20 per cent 3 cc, 5 cc and 10 cc ampuls

U S trademark 315 083

CHAPTER XII

CONTRACEPTIVES

When protection from pregnancy is considered advisable, contraceptives are used to prevent passage of active spermatozoa from the vagina into the uterus. This is accomplished as follows:

| | |
|-----|------------------------|
| " " | as diaphragms, which |
| " " | must travel to reach |
| " " | osure to a spermicidal |
| " " | d creams act as chem |
| " " | with which they come |
| " " | ney they also have an |

obstructive function. Certain accessory devices are used with these, such as inserters and extractors for the diaphragms and syringe applicators for the jellies and creams. In control of conception acceptability probably plays a greater role in the use and therefore the effectiveness of a prescription than in most fields of medicine. The esthetic block or reluctance toward various methods differs with different users, and variation of method by a single user is often found to lead to greater acceptability and consequently a higher degree of protection.

When contraceptive preparations are prescribed the physician should warn that there must be strict adherence to his directions. To do otherwise invites decrease in expected effectiveness. No one method can be guaranteed as being 100 per cent effective, although a high degree of protection can be expected if the patient has been properly examined and informed by the physician. The status of conception control has been reviewed in a report of the Council which appeared in *The Journal*, Dec 18 1943, p 1043.

Criteria for Acceptability of Contraceptive Jellies, Creams and Other Chemical Agents and of Syringe Applicators and Nozzles

For guidance in reviewing contraceptive products, the Advisory Committee on Contraceptives of the Council on Pharmacy and Chemistry has proposed the following criteria. These have been adopted by the Council but it should be emphasized that they may be changed from time to time. As the experience of the committee and the Council grows, improvements may appear desirable.

1 The use of the word 'contraceptive' need not be limited to materials which will prevent conception on every occasion of use.

2 Evidence shall be furnished that use of the material decreases the incidence of pregnancy. This evidence may be secured in connection with occlusive devices unless the manu-

facturer's advertising is directed chiefly toward the use of the jelly or cream without such devices. It is desirable that each case reported should be observed for at least twelve months and that the minimum of 75 patient years of experience should be reported. If cases are excluded from the series on the basis of their being irregular users the number excluded and the nature of the evidence justifying their exclusion should be stated.

3 Evidence shall be submitted that 100 or more couples have used the material on six or more occasions without subjective injury.

4 Evidence shall be submitted that 12 or more women have received vaginal applications of the recommended dosage on twenty one successive days without subjective irritation or injury and without evidence of physical damage shown on speculum examination by a physician with special experience in this field. Inspection of the vagina once a week should be done as a protection to the patient in case the jelly proves to be irritating.

5 The quantitative formula from which the contraceptive mixture is prepared shall seem to the Advisory Committee to be safe and presumably, effective.

6 The consistency shall be satisfactory to the committee. It shall not show separation into more liquid and more solid portions visible to the naked eye.

7 Evidence shall be submitted that the consistency is not substantially changed after storage for twelve months at 27° C.

8 The consistency shall be reasonably uniform from batch to batch.

9 The spermicidal time of the contraceptive material as measured by the method of Brown and Gamble (*Human Fertil* 5:97 [Aug.] 1940) with proportions of material isotonic solution of sodium chloride and semen of 1:4:5 shall be thirty minutes or less as measured by the average of four or more tests.

10 The use of jellies or creams suggested by the manufacturer need not be limited to use in conjunction with an occlusive device.

11 If a syringe applicator or nozzle is furnished for use in connection with the jelly or cream it shall be sufficiently translucent to permit the detection of air which might lead to inadequate dosage.

Criteria for Acceptability of Contraceptive Diaphragm or Cap

1 The advertising and direction of the manufacturer should make it clear that contraceptive diaphragms are intended for use in conjunction with a spermicidal jelly or cream.

2 The manufacturer's advertising must not state or imply that the appropriate diaphragm can be chosen without the aid of a physician

3 Evidence must be submitted that the diaphragm will last under ordinary conditions of contraceptive use for twelve months or more without perforations or other defects

4 With each diaphragm should be packed directions warning the user not to expose it to ordinary oils or greases unless evidence is submitted that the material of which the diaphragm is made is not damaged by these substances

5 The design shall be satisfactory to the committee

6 The directions packed with each diaphragm shall include instructions to the user to inspect the diaphragm from time to time for holes or tears and discard the diaphragm if one is present

Contraceptive Preparations

CONTRACEPTIVE CAPSULES AND SUPPOSITORIES

Actions and Uses—A convenient method for introducing contraceptive material into the vagina without the need of an apparatus is the use of capsules converted to a jelly or liquid form in order to cover the requisite area, hence prompt liquefaction is important. For some suppositories this results from a melting point below the temperature of the body. For others the active material is enclosed in a gelatinous shell which melts or opens when exposed to body temperature and moisture. The time required should be under ten minutes, and the users should be instructed to allow this time to elapse before intercourse. A douche should not be taken within six hours after ejaculation.

To insure further protection physicians may advise the concurrent use of an occlusive device such as a diaphragm (concerning which see general statement)

PERNOX, INC

Pernox Vaginal Capsules A soft gelatin capsule containing a low melting mass prepared from the formula

| | |
|------------------------------|----------|
| Rienoleic acid | 45 mg |
| Propylene glycol monoacetate | 1.830 Gm |
| Woolfat fraction | 2.200 Gm |
| Wetting agent | 45 mg |
| Propylene glycol | 0.183 Gm |
| Tragacanth | 0.214 Gm |

Actions and Uses—See preceding article

Dosage—One capsule containing 45 Gm

CONTRACEPTIVE JELLIES AND CREAMS

Actions, Uses and Dosage—Jellies and creams for contraceptive use are introduced into the vagina usually with an occlusive diaphragm or cervical cap, not more than twelve hours before sexual intercourse. When so used a portion of the dose of jelly or cream may be placed within the vagina and between the occlusive device and the cervix. The jelly or cream is usually inserted by a special plunger type of device. The remainder of the jelly or cream should then be placed in the cervical area of the vagina adjacent to the occlusive device.

Jellies and cr

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before interco

dose varies but is usually approximately 5 cc. To allow adequate time for chemical immobilization the occlusive device should not be removed nor should a douche be taken within six hours after ejaculation.

As most c

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creams used

of rubber

jellies and

Applicators are designed for ready filling from the container of contraceptive jelly or cream. They should be of such pressure of the recommended type which might lead to irritation of the vagina. They should be sufficiently thick to prevent the vagina extremely impure. They should be sufficiently large to prevent entry into the urethra.

CONTRA CREME AND DIAPHRAGM CO

Contra Creme 635 Gm collapsible tubes. A stearic acid cream having a pH of 7.3 packaged from the formula

| | |
|------------------------|--------|
| Phenylmercuric acetate | 0.06% |
| Triethanolamine | 0.06 |
| Glycerin | 2.5 |
| Glycol monostearate | 3.5 |
| Stearic acid | 12.0 |
| Diluted water to make | 100.00 |

Packaged with a Contra Applicator or in refill packages containing a tube of cream only.

U. S. trademark 355,838

Actions, Uses and Dosage—See preceding article Contraceptive Jellies and Creams.

Contra Creme

Insert the Contra Applicator into the threaded plastic syringe threaded screw onto the tubes of Contra Creme. The full dose

ORTHO PHARMACEUTICAL CORP

Ortho-Creme—78 Gm collapsible tubes A nonfatty stearic acid cream having a pH of 6, prepared from the formula

| | |
|-----------------------|---------|
| Stearic acid | 24.00% |
| Cetyl alcohol | 0.50 |
| Glycerin | 8.00 |
| Ricinoleic acid | 0.75 |
| Sodium lauryl sulfate | 0.78 |
| Boric acid | 2.00 |
| Triethanolamine | 0.25 |
| Perfume | 0.05 |
| Water to | 100.00% |

Packaged with an Ortho Vaginal Applicator or in refill packages containing a tube of cream only

U S trademark 390 141

Actions, Uses and Dosage—See preceding article Contraceptive Jellies and Creams

Ortho-Gynol Vaginal Jelly—92 Gm collapsible tubes A water soluble jelly formed from tragacanth and acacia having a pH of 4.5 prepared from the formula

| | |
|--|---------|
| Tragacanth | 3 |
| Acacia | 2 |
| Glycerin | 10 |
| Boric acid | 3 |
| Ricinoleic acid | 0.75 |
| Propyl ester of parabhydroxybenzoic acid | 0.05 |
| Oxyquinoline sulfate | 0.025 |
| Perfume | 0.025 |
| Water to | 100.00% |

The consistency is indicated by a 50.55 mm dart penetration at 40 C when tested with the Braun dart penetrometer

Packaged with an Ortho Vaginal Applicator or in refill packages containing a tube of jelly only

U S patent 2 330 846 (Oct 5 1943 exp res 1960) U S trademark 298 222

Actions, Uses and Dosage—See preceding article Contraceptive Jellies and Creams

Ortho Vaginal Applicator A transparent plastic syringe threaded at the blunt, intravaginal end to screw onto the tubes of Ortho Gynol Vaginal Jelly or Ortho Creme, to permit filling by compression of the tube The full capacity is 5 cc, the recommended dose

U S trademark 394 998

WHITTAKER LABORATORIES, INC

Cooper Creme 75 Gm collapsible tubes A white non greasy, water miscible stearate cream having a pH of 7.3 prepared from the formula

| | |
|--------------------------------------|-------|
| Trioxymethylene U S P | 0.04% |
| Sodium oleate | 0.67 |
| Stearic acid | 23.04 |
| Aqua | 65.50 |
| Trihydroxyethylamine | 7.91 |
| Dioctyl sodium sulfo succinate | 0.50 |
| Hydrous aluminum silicate | 2.34 |
| Perfume (compounded oil of lavender) | q. s. |

Packaged with a Cooper Creme Dosimeter or in refill packages containing a tube of cream only

Actions Uses and Dosage—See preceding article, Contraceptive Jellies and Creams

Cooper Creme Dosimeter A transparent plastic tube threaded at the blunt intravaginal end to screw onto the tubes of Cooper Creme to permit filling by compression of the tube. The full capacity of the dosimeter is 10 cc.

CONTRACEPTIVE DIAPHRAGMS

Actions and Uses—As diaphragms cannot be designed to form a junction with vaginal wall or cervix which will prevent the passage of an organism of the size of a spermatozoon a spermicidal jelly or cream should be prescribed for use with them.

The appropriate size of diaphragm (varying from 50 to 105 mm in diameter) must be chosen for each user. It should be as large as is comfortable, large enough to extend easily over the cervix, anchoring posteriorly in the posterior fornix and anteriorly behind the symphysis. The appropriate size may change after a delivery and during the postpartum months. Satisfactory fitting is not possible in some cases of variant anatomy of the soft parts (this does not refer to bony structure).

The diaphragm and jelly or cream should be inserted before intercourse (not more than twelve hours before) and left in place until six hours or more after ejaculation (not more than thirty six hours). Rubber diaphragms should not be exposed to fatty substances and should be inspected from time to time for holes or tears.

ORTHO PHARMACEUTICAL CORP

U S trademark 387 080

Ortho Diaphragms Latex rubber diaphragms covering a circular coiled spring the external diameter varying in gradations of 5 mm from 55 to 95 mm.

JULIUS SCHMID, INC

Ramses Diaphragms Gum rubber diaphragms covering a circular spring the external diameter varying in gradations of 5 mm from 50 to 95 mm

U S Patent 2 024 539 U S Trademark 284 083

CONTRACEPTIVE DIAPHRAGM INSERTERS

Uses—Inserters are designed to stretch the circular spring of a contraceptive diaphragm into a long oval and to furnish a handle with which it may be inserted into the vagina and guided beyond the cervix. To some users they have the esthetic appeal that they minimize digital contact with jelly or cream or genitals

JULIUS SCHMID, INC

U S patent 2 257 212 U S trademark 353 028

Ramses Diaphragm Introducer A transparent plastic device designed to stretch and hold for insertion a diaphragm of a given size. Made in different sizes marked for diaphragms from 50 to 90 mm in diameter in gradations of 5 mm. On the handle end is a blunt hook to assist in extracting the diaphragm

CONTRACEPTIVE FITTING RINGS

Uses—To enable the physician to test the size of contraceptive devices needed for a given patient circular coiled springs of the various sizes have been prepared without the thin rubber diaphragm. As these have thick rubber coatings repeated sterilization by boiling is possible without deterioration

JULIUS SCHMID, INC

Ramses Fitting Rings Prepared in sets having sizes from 50 to 90 mm in diameter in gradations of 5 mm

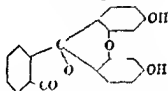
CHAPTER XIII

DIAGNOSTIC AIDS

External

FLUORESCEIN — **Fluoresceinum** — **Resorcinolphthalein** (a term not strictly correct but commonly used) — **Dioxy fluoran** — The anhydride of fluoresceinic acid

Fluorescein is formed by combining resorcinol ($C_6H_4(OH)_2$) with phthalic anhydride ($C_6H_4 < \begin{smallmatrix} CO \\ >O \end{smallmatrix} > O$), water is eliminated and the product has the following structural formula



Fluorescein is closely related to phenolphthalein and its derivatives, differing chiefly in the presence of an oxygen molecule linking the two ortho positions of the phenol nuclei. In common with the phthaleins, it forms salts with alkali whereby a rearrangement takes place and the quinoid group is formed. Fluorescein is easily brominated the tetrabrom compound being the beautiful dye eosin.

Actions and Uses — The soluble sodium salt of fluorescein (fluorescein 2 Gm, sodium bicarbonate 3 Gm, water to make 100 cc) has been used for the diagnosis of corneal lesions and the detection of minute foreign bodies embedded in the cornea. While a weak solution of fluorescein will not stain the normal cornea, ulcers or parts deprived of epithelium will become green and remain so for a time. Foreign bodies will appear surrounded by a green ring, loss of substance in the conjunctiva is indicated by a yellow hue. Fluorescein also reveals defects or disease of the endothelium of the cornea producing a deep coloration of the diseased area.

Preparation and Tests —

Fluorescein is prepared by the fusion of phthalic anhydride and resorcinol at from 195 to 200 C till the mass becomes solid. This is extracted with water and the residue dissolved in potassium hydroxide solution, which is then filtered and the fluorescein precipitated with acid.

Fluorescein is an orange red powder insoluble in water, ether, chloroform and benzol, soluble in hot glacial acetic acid and boiling alcohol. It dissolves in alkaline solution with formation of a salt. The alkaline solution by transmitted light is red, by reflected light it has a green

fluorescence even in very dilute solution. When fluorescein is boiled with chalk and water the calcium salt of fluorescein is formed which is recognized by its red brown color and green sheen.

MERCK & CO., INC.

Fluorescein (Powder)

Internal

Benzoic Acid Derivatives

SODIUM BENZOATE.—When dried at 100 C. for six hours contains not less than 99 per cent of $\text{C}_6\text{H}_5\text{COONa}$
U S P

For standards see the U S Pharmacopeia under Sodium Benzoate

Actions and Uses.—The intravenous use of sodium benzoate as a liver function test was suggested by Quick and his co-workers in 1938 (Quick A J, Ottenstein H N and Weltcheck Herbert *Proc Soc Exper Biol & Med* 38 77 [Feb 1 1939]).

The test is contraindicated in the presence of renal disease because here the hippuric acid is but partially eliminated.

Dosage.—The bladder is emptied before administration of the drug. Inject *slowly* intravenously 20 cc of sodium benzoate solution containing 1.77 Gm of the salt (equivalent to 1.5 Gm of benzoic acid) using not less than five minutes for the injection. Exactly one hour after the injection a complete urine specimen is collected and the amount of hippuric acid determined by the method of Quick and his co-workers. *Am J*

Gm of
) within

GEORGE A. BREON & COMPANY, INC.

Sodium Benzoate Solution 1.77 Gm (equivalent to 1.5 Gm benzoic acid) in 20 cc ampuls

Barium Sulfate

BARIUM SULFATE.—For description and standards see the U S Pharmacopeia under Barium Sulfate

Caution.—When Barium Sulfate is prescribed the title should always be written out in full to avoid confusion with the poisonous barium sulfide or sulfite U S P

Actions Uses and Dosage —Barium sulfate for roentgen examination being freed from soluble barium and other salts passes unchanged through the digestive tract and because of this is used in taking roentgenograms of the stomach and of the intestines

For Roentgen Examination of the Stomach —A barium sulfate suspension is made containing 750 Gm of barium in 1500 cc in 400 cc of water

For Roentgen Examination of the Colon —A barium sulfate suspension is made containing 750 Gm of Barium in 1500 cc of water

The patient should be prepared by the administration of 1 ounce of castor oil the night before the examination and of a plain water or saline enema two hours before the procedure is performed

The suspension warmed to body temperature is injected into the rectum by enema tube from a height of 90 to 180 cm

MALLINCKRODT CHEMICAL WORKS

Barium Sulfate for X Ray Diagnosis bulk

MENCK & Co, Inc

Barium Sulfate for X-Ray Diagnosis bulk

Skiabaryt for Oral Administration A mixture of barium sulfate 80 to 85 per cent sugar tragacanth vanillin cinnamon and cacao

U S trademark 165 022

Dosage Tr turate 150 to 200 Gm w it cold water added gradually to form a smooth thin paste then add warm water gradually until the mixture measures 500 cc The mixture is then ready for drinking

Skiabaryt for Rectal Administration A mixture of barium sulfate U S P 80 to 85 per cent sugar and tragacanth

Dosage Mix 200 Gm with cold water to form a smooth paste then add warm water with stirring until the mixture has acquired a fairly fluid consistency It is then ready for administration through the irrigator

Iodized Oils

Iodized oils are injected as contrast mediums in roentgen diagnosis especially of tumors of the spinal cord in the localization of bronchial and pulmonary lesions and in gynecology Various vegetable oils may be used animal oils cause local irritation According to the method of iodation the oil may contain iodine alone or iodine and chlorine (chloriodized oils) These do not differ essentially

Iodized oils are quite viscid For injections into cavities they may be rendered less viscid by the addition of ethyl oleate they may be rendered water miscible by emulsification

Boil 0.5 cc. of lipiodol 40% iodine and 10 cc. of alcoholic solution of potassium hydroxide (1 in 10), in a porcelain dish for about five minutes, evaporate the liquid on a water bath and ignite the residue. Dissolve the residue in 10 cc. of water, filter the solution, add 5 cc. of hydrochloric acid to the filtrate, then add chloroform and a few drops of chlorine water and agitate. The chloroform solution is violet. Dissolve 1 cc. of lipiodol 40% iodine in 10 cc. of phenolphthalein solution. Add 10 cc. of potassium hydroxide solution. The lipiodol 40% iodine parent liquid results.

Boil about 1 cc. of lipiodol 40% iodine with 10 cc. of nitric acid and 0.5 Gm. of silver nitrate, cool, add 25 cc. of water, collect the precipitate formed on a filter paper, wash free from the excess of silver nitrate, puncture the filter, collect its contents in a glass stoppered flask, treat with 50 cc. of stronger ammonia water, agitate thoroughly and allow to stand for one hour. Filter off the insoluble silver iodide, treat the filtrate with 15 cc. potassium iodide solution and remove the excess of ammonia by evaporation on a steam bath. No opalescence results (absence of chlorine compounds).

Ignite about 1 Gm. accurately weighed. The residue does not exceed 0.01 per cent. Transfer about 0.35 Gm. accurately weighed to a bomb tube, determine the iodine content by the Carius method. The amount of iodine found is not less than 39 per cent nor more than 41 per cent.

E. FOUQUERA & COMPANY, INC.

Lipiodol, 40% Iodine. 1 cc., 2 cc., 3 cc. and 5 cc. ampuls and 20 cc. neoprene capped flask.

Lipiodol 40% Iodine Radiologique Descendant. 5 cc. flasks.

U. S. trademark 196 479

LIPIODOL RADIOLOGIQUE ASCENDANT.

Iodized Poppy-Seed Oil 10 per cent.—An iodine addition product of poppy-seed oil containing 9.8 to 11.2 per cent of iodine (0.11 Gm. of iodine per cc.) in organic combination.

Actions and Uses.—Lipiodol radiologique ascendant is used for recognition of intradural tumors when it is desired to employ a contrast medium of lesser density than that of the spinal fluid.

Dosage.—From 1 to 2 cc., previously brought, with the syringe, to a temperature of 40° C.

Tests and Standards.—

Lipiodol radiologique ascendant is a yellow, oily liquid, which possesses an alliaceous odor and an oleaginous taste, and is insoluble in water. On exposure to air and sunlight it decomposes, turning brown in color. Its specific gravity at 20° C. is from 0.99 to 1.

Lipiodol radiologique ascendant conforms to the tests for identity and purity, ash and assay as described under lipiodol except that the iodine content found is not less than 9.8 per cent nor more than 11.2 per cent.

E. FOUQUERA & COMPANY, INC.

Lipiodol Radiologique Ascendant. 5 cc. flasks.

U. S. trademark 196 479

Ethyl diiodobrassidate
of diiodobrassic acid
containing 41 per cent

Actions and Uses—Lipiodine is used as a substitute for the inorganic iodides and as a contrast medium for roentgenologic work. See preceding article Iodized Oils.

For diagnostic work, from 5 to 20 cc. of lipiodine diagnostic as determined by the extent of the field to be investigated.

Tests and Standards—

Lipiodine crystallizes in white odorless and tasteless needles melting at 37° C. It is insoluble in water, slightly soluble in alcohol and very soluble in fatty oils, ether and benzene. Lipiodine is decomposed by exposure to direct light.

The iodine content of lipiodine is from 40.5 per cent to 41.5 per cent.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Lipiodine Diagnostic 10 cc. bottle. A 60 per cent solution of lipiodine in sesame oil.

U. S. patent 1,624,171 (April 23, 1912, expired)

U. S. trademark 81,554

Water Soluble Organic Iodine Compounds for Roentgenography

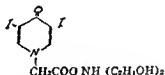
Satisfactory roentgenograms of the urinary tract may be secured by the intravenous injection of soluble iodine compounds of low toxicity, which are rapidly excreted by the urine. Several organic compounds are now available for this use. Sodium iodide, in the necessary dose, is too toxic for intravenous injection. The organic compounds may also be used for ureteral retrograde pyelography.

For intravenous urography it is now generally accepted that no fluids should be given to the patient for several hours (usually from midnight) prior to examination. Restriction of fluids permits greater concentration of the drug. The gastrointestinal tract should be cleared of gas and retained materials by enemas and laxatives, preferably of castor oil. The excretory urogram should be made by those who are experienced with this method and during the entire procedure the patient should be watched for untoward reactions. Recently, Asher and Harris have described an ocular test for sensitivity to diodrast, (*Am. J. Roent.* 48:762, 1942). The medium should be given slowly, pausing after 1 or 2 cc. are injected to see if a reaction may occur. Care should be exercised to ensure that all the solution is injected into the vein. Side effects which may be encountered include flushing of the face and neck, urticaria, fall in blood pressure, nausea, vomiting, lacrimation, salivation, edema of the glottis, bouts of coughing, tight feeling, or choking sensation and cyanosis. Usually these symptoms disappear over varying

periods of time but fatalities have been encountered. Any history of allergy should be elicited before injection. If there is reason to suspect that a reaction may occur a small initial dose may be given first. In any event, epinephrine hydrochloride 1:1000 should be available when the injection is made. The intravenous use of the drug is contraindicated in patients with severe liver disorders, nephritis and severe uremia and it should be used with caution in cases of active tuberculosis and of hyperthyroidism. Excretory urography should not be used routinely in all patients. Further, this method may have to be checked with retrograde pyelography, and either or both methods closely correlated with the clinical findings. Injection of the medium into the kidney pelvis is most accurately gauged by using a manometer, but lacking this instrument gravity or a syringe may be used. After excretory urography or retrograde pyelography should not be repeated too soon.

The compounds may be used for venograms in the study of varicose veins.

DIODRAST—Trade name
—Diodrast contains



Actions and Uses—Diodrast is used as a contrast agent for intravenous urography. Local reactions about the site of injection are absent or very mild, systemic reactions occur occasionally. The latter consist chiefly of flushing of the skin with a sense of warmth, less often transient nausea, vomiting, erythematous eruptions, respiratory distress and cyanosis. These side effects usually subside within a few minutes to an hour or so without special therapy but the skin eruptions may rarely persist for several days. In animals diodrast in doses equivalent by weight to those used clinically has been found to lower the blood pressure for a period of about two hours; this slowly returns to normal and may be followed by a secondary rise. Respiration is stimulated. These actions have been reported also to occur in human subjects. Fasting and dehydration of patients preliminary to injection of the drug are widely employed. The optimum time for taking roentgenograms varies between five and fifteen minutes after injection in individuals with normal kidney function (usually one exposure is made after ten minutes and a second after a further interval).

of ten or fifteen minutes) When renal function is impaired this interval is proportionately longer (thirty minutes or more)

blood pressure would be dangerous

Dosage—Diodrast is usually administered intravenously in the form of an aqueous solution, each cubic centimeter contains 0.35 Gm. Twenty cc of a solution containing 7 Gm of diodrast previously warmed to body temperature, is injected slowly usually into the cubital veins. Children are given correspondingly smaller doses. It may be administered intramuscularly or subcutaneously in infants, children and adults with inaccessible or obliterated arm veins and sometimes in uncooperative, restless patients. For subcutaneous injection the adult dose (20 cc) is diluted with 80 cc normal saline solution. 50 cc of this mixture are injected subcutaneously over each scapula. For intramuscular injection the dose ranges from 10 cc to 20 cc in children and from 20 cc to 30 cc in adults. One half of the amount decided upon is injected into the right buttock and the other half into the left buttock. To prevent local discomfort a local anesthetic may be used if needed.

Tests and Standards—

Diodrast responds to the following identity tests. Dilute about 10 cc of diodrast solution with an equal volume of water, add an excess of diluted hydrochloric acid, collect the liberated 3,5 diiodo 4 pyridene *N*-acetic acid on a filter paper, wash and dry at 100°C. it melts with decomposition between 245 and 249°C. (the melting point bath previously used for the test).
 0.1 Gm. of the substance, after the test tube contents are allowed to stand for a few minutes, to one portion of 1 cc of insoluble in an excess of stronger ammonia water, to the other portion add a few drops of fresh ferrous and ferric sulfate solutions, heat to nearly boiling and carefully neutralize with diluted hydrochloric acid, a finely divided blue precipitate results. Concentrate the original filtrate from the foregoing, cool in ice water, filter, evaporate to syrupy consistency, add 5 cc of alcohol, neutralize the mixture carefully, and filter with absolute alcohol to boiling and lamne trinitrophenol and dry in a desiccator, it melts at 109 to 110°C.

Dissolve about 1 Gm of the resultant acid in 15 cc. of a 10 per cent solution of sodium hydroxide and make up to a volume of 3 cc. a clear colorless solution results. To the foregoing solution add 7 cc. of water and an excess of diluted hydrochloric acid, filter, and divide the filtrate into two portions, to one portion add 1 cc. of chloroform

powder, slightly soluble in water, slightly soluble in organic solvents. It melts at 245 to 249 C., with decomposition (the melting point bath previously heated to 200 C.).

Diiodo-4 pyridone-N acetic acid responds to identity and purity tests previously described under diodrast, except those dealing with diethanol amine.

DIODRAST STERILE SOLUTIONS. Diodrast solution is prepared by neutralizing 3,5 diiodo-4 pyridone-N acetic acid in water with an equal molecular quantity of diethanolamine (not isolated).

Diodrast solution is neutral to litmus. It is

The specific gravity of diodrast solution, accurately measured, in a suitable bath and ignite

red, to a 100 cc. add 10 cc. of the boiling and add filtrate. Stir until or thirty minutes in crucible, using spicate with 5 cc. To the weight of etc acid) found. Itant is not less

WINTHIROP CHEMICAL COMPANY, INC.

Diodrast Sterile Solution (35 per Cent, W/V): 10 cc., 20 cc., and 30 cc. ampuls

U. S. patent 1,993,039 (March 5, 1935; expires 1952). U. S. trade mark 312,451.

DIODRAST COMPOUND SOLUTION.—An aqueous solution containing approximately 40.5 per cent (W/V) of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid and approximately 9.5 per cent (W/V) of the diethylamine salt of

3,5 diodo 4 pyridone N-acetic acid. Diodrast compound solution contains about 25 per cent (W/V) of iodine in organic combination.

Actions and Uses—Diodrast compound solution is employed for roentgenographic visualization of the urinary tract by intravenous injection or by direct injection into the renal pelvis through a ureteral catheter. It is designed to provide a relatively large amount of iodine in a small volume of solution particularly for injection of obese subjects or for patients who cannot or will not take excretion urography. . . .
 taken at 5, 15 and . . .

Delayed, incomplete or absent shadows are given the same interpretation as when diodrast is employed. The same contraindications and precautions should be observed as for diodrast.

Dosage—For excretion urography, diodrast compound solution is administered intravenously in sterile aqueous solution the average dose for adults being 20 cc. Diodrast compound solution may be employed without dilution for retrograde pyelography. For emergency methods of administration see literature.

Tests and Standards—

Diodrast compound solution is prepared by neutralizing 3,5 diodo-4 pyridone-N-acetic acid in water with appropriate quantities of diethanolamine and diethylamine. The mixture thus formed (not isolated in solid form) is soluble in water.

Diodrast compound solution occurs as a clear, pale yellow, odorless liquid possessing a bitter taste. It is neutral to litmus and is incompatible with mineral acids and heavy metal salts. Its specific gravity is about 1.270 at 25°C.

Dilute about 0.5 cc. of diodrast compound solution to 5 cc. with water and acidify with hydrochloric acid; collect the precipitate on a filter, wash with cold water and dry at 100°C. The 3,5 diodo-4 pyridone N-acetic acid obtained melts at 245-249°C., with decomposition (the melting point bath previously heated to 200°C.).

Dilute about 10 cc. of diodrast compound with 20 cc. of water, acidify with hydrochloric acid and filter off the precipitate. To the filtrate add 3 cc. of approximately 50% sodium hydroxide solution and distill into about 25 cc. of normal hydrochloric acid. Evaporate the solution containing the distillate to dryness on a water bath, recrystallize the residue from alcohol by the addition of diethyl ether, dry the product under partial vacuum; the melting point of the diethylamine hydrochloride obtained is from 224 to 227°C., with sublimation.

Acidify the alkaline residue remaining in the distilling flask with . . . the flask and evaporate . . . the filtrate and concentrate the residue with 5 cc. . . . sodium hydroxide . . .

filter, wash and finally dilute the filtrate to about 8 cc with alcohol. Add about 0.5 Gm of *picric acid* (*trimetaphenol*) to the solution, boil cool and place in the ice chest. Collect the precipitate on a filter recrystallize from absolute alcohol and dry under partial vacuum. The melting point of the diethanolamine trimetaphenolate obtained is between 109 and 110 C.

Dilute 20 cc of diodrast compound solution, accurately measured to 200 cc in a calibrated flask. Use portions of the diluted solution in the following determinations.

Evaporate 20 cc of the diluted solution, accurately measured in a tared platinum dish on a water bath and dry to constant weight at 100 C. the weight of the residue is equivalent to not less than 48 per cent (W/V) nor more than 51 per cent (W/V) calculated to the original solution. Ash the residue in the presence of sulfuric acid the weight of the ash is not more than 0.1 per cent.

Transfer 20 cc of the diluted solution to a distillation apparatus, add 50 cc of 10 per cent sodium hydroxide and distil into 30 cc of 10 per cent sodium hydroxide. The rate of distillation should be such that the red color of the indicator changes to blue as the distillation proceeds. The amount of tenth normal hydrochloric acid consumed by the distillate is equivalent to the ammonia derived from the original solution.

Acidify the residue remaining in the Kjeldahl flask used in the foregoing determination with sulfuric acid. Concentrate the mixture and digest with 10 cc of sulfuric acid and 0.05 Gm of selenium metal until clear. Cool, dilute with 100 cc of water, transfer to the ammonia distillation apparatus and add an excess of 50 per cent sodium hydroxide. Distil into 50 cc of tenth normal hydrochloric acid and titrate the excess acid with tenth normal sodium hydroxide using methyl red as the indicator. The amount of tenth normal hydrochloric acid consumed by the distillate is equivalent to the ammonia derived from the original solution.

to the original solution.

From the titration of the distillate with tenth normal sodium hydroxide, calculate the amount of tenth normal hydrochloric acid found. Calculate the difference between the amount of tenth normal hydrochloric acid found and the amount of tenth normal hydrochloric acid consumed by the distillate. The difference is not less than 8.2 per cent.

WINTHROP CHEMICAL COMPANY, INC

Diodrast Compound Solution 20 cc ampuls

U S patent 1,993,039 (March 5 1935 expires 1952) U S trade mark 312,451

DIODRAST CONCENTRATED SOLUTION—An aqueous solution containing 70 per cent (W/V) of the diethyl amine salt of 3, 5 diodo 4-pyridone-N acetic acid.

Actions and Uses—Diodrast concentrated solution is employed for use in a special diagnostic procedure for visualization of the heart, the ascending and descending aorta and branches the

superior vena cava the pulmonary artery and branches the coronary arteries and other structures of the heart and mediastinum. It has also been used for cholangiography by injection of the material into the common bile duct. The technic in using this agent is relatively complicated and requires accurate timing and teamwork between the physician the patient and the roentgenologist. The method consists in injecting the substance into the blood and taking roentgenograms simultaneously with the concentration of the opaque material in the cardiopulmonary system. In addition a preliminary examination of the chest with the x rays is necessary to obtain data for roentgenography. At times it is necessary to determine

contraindications

thyroidism

of heart disease

who are critical

tests and determine

carried out. Those with an idiosyncrasy should not be given the drug. To lessen nausea and vomiting the stomach should be empty. Side effects include dizziness nausea vomiting sense of intense warmth sweating pallor hypotension transient pain at the site of injection headache fever chills cyanosis etc. Delayed reactions may occur. Premedication with a barbiturate is advisable. epinephrine is administered when there is a possibility of an allergic reaction or low blood pressure. This technic can be mastered by experienced workers who have the proper facilities although it might be dangerous in the hands of persons who are inexperienced or by those who use the technic in a casual manner. In skilled hands untoward reactions are comparatively few. It is claimed by the manufacturer that this agent is sufficiently stable to permit boiling for a short time if a question of sterility should arise although the product is marketed in sterile form.

Dosage—Diodrast concentrated solution should not be used for ex-

be used

diagnosis

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45 cc

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minute

from 0

not be

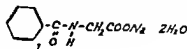
result. If crystals are present warm solution to body temperature before using.

For cholangiography the amount of Diodrast concentrated solution varies within wide limits as little as 15 cc and as much as 100 cc has been required by direct injection into the common bile duct.

WINTHROP CHEMICAL COMPANY, INC

Diodrast Concentrated Solution (70 per Cent W/V)
50 cc vial

HIPPURAN—Sodium ortho-iodohippurate— $C_6H_4I CONHCH_2COONa + 2H_2O$ The sodium salt of *o* iodohippuric acid. Hippuran contains 34.95 per cent of iodine, or 38.8 per cent when calculated to the dried substance



Actions and Uses—Hippuran is proposed for use as a radiopaque agent for intravenous oral or retrograde urography. When used by the intravenous route irritation at the site of injection is stated not to occur and systemic reactions appear to be unusual, a sensation of generalized warmth is the most common side effect nausea occurs occasionally and vomiting rarely. Fasting and dehydration of patients preliminary to administration of the drug are usually employed. Pressure over the bladder region is employed by some clinicians this is released immediately before the first exposure and is replaced until the next. Ordinarily the first film is exposed about ten minutes after injection and two subsequent pictures are taken at fifteen or twenty minute intervals. In case excretion is delayed later exposure may be necessary.

Results with oral administration of the drug are less satisfactory but a sufficiently high percentage of successful pictures appear to be obtained to make this method worthy of trial in occasional cases in which intravenous or retrograde urography is not feasible. The somewhat objectionable taste of the compound usually does not militate against its ingestion. Toxic effects after oral administration have not been reported. Pictures are taken 60 90 120 and 150 minutes after oral administration. The use of moderate compression over the bladder region is recommended in the intervals between exposures. While the iodine in hippuran is firmly bound the compound should nevertheless be used with caution in patients with hyperthyroidism and tuberculosis. The intravenous use of the drug is contraindicated in severe liver disorders nephritis and uremia. In suspected cases preliminary hepatic and renal function tests should be employed.

Satisfactory visualization has been reported with hippuran when employed by the retrograde method for urethrograms cystograms or pyelograms. There is said to be little or no tissue irritation with effective concentrations.

Dosage—For intravenous use 25 cc of a solution containing 12 Gm of hippuran previously warmed to body temperature is injected into the cubital vein. Young children are given

proportionately smaller doses. For oral use, 12 Gm of hippuran is dissolved in 75 cc of simple syrup. For children, 10 Gm is employed in 15 to 5 per cent solution either by diluting with water or by dissolving in water and sterilizing by heat.

Tests and Standards.—

Hippuran occurs as a white, crystalline powder, possessing a faint odor and an alkaline taste; very soluble in water, freely soluble in ethyl alcohol and soluble in dilute alkali. An aqueous solution is neutral or faintly alkaline to litmus.

Fuse about 0.2 Gm of hippuran with 2 Gm of powdered sodium hydroxide; it decomposes with the evolution of iodine vapors and ammonia. Dissolve about 0.5 Gm of hippuran in 100 cc of water, add an excess of diluted hydrochloric acid, collect the resultant α -iodo-hippuric acid on a filter, wash and dry at 110°C. It melts at 171 to 174°C; to 1 cc. of the foregoing filtrate add 10 cc of uranyl zinc acetate solution, a yellow precipitate results. Transfer about 0.5 Gm of hippuran to a glass-stoppered cylinder, add 25 cc of a diluted nitric acid (one part diluted nitric acid and 5 parts water), shake for five minutes, filter; the filtrate yields no distinct opalescence on the addition of 5 cc of 10 per cent barium chloride solution.

If water, add 5 cc

of 10 cc each of

cc of barium chlo-

ride on saturation

weighed to constant weight

more than 10 per cent nor less

hippuran, accurately weighed

replacing the evaporated

liquid if necessary, decant the supernatant liquid through filter paper and wash filter with 10 cc and 5 cc portions respectively, evaporate

MALLINCKRODT CHEMICAL WORKS

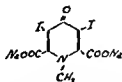
Hippuran (Powder): bulk

Hippuran Crystals: 12 Gm, 100 and 500 Gm bottles

Sterile Solution Hippuran: 12 Gm in 25 cc

U S patent 2,135,474 (Nov 1 1938 expires 1955) U S trademark

NEO-IOPAX.—Neo-Iopax Sodium—Disodium *N* methyl
3, 5-diiodo 4-
COONa Th
acid Neo-Ic



Actions and Uses—Neo iopax is used as a contrast medium in intravenous urography and retrograde pyelography. Clinical reports indicate that systemic reactions occur uncommonly and are usually mild and fleeting. In some cases there is more or less severe pain in the arm radiating to the shoulder, usually this disappears on completion of the injection but in a small percentage of cases it may persist for a variable period. The pain may usually be relieved by local applications of heat and the administration of an analgesic when necessary. Fluid intake should be restricted for about twelve hours prior to the examination. If only anatomic information is desired, it is usually sufficient to take a single roentgenogram from ten to twenty minutes after injection. In other cases, a series of roentgenograms are taken at intervals of five, fifteen and thirty minutes after injection. It is advisable to take a film over the urinary bladder area when making the roentgenogram thirty minutes after the injection. If the first plates show that but little of the drug has been excreted, it is presumed that the kidneys are functioning poorly, and several hours should be allowed to elapse, during which plates should be made at intervals. Impairment of renal function will allow but poor concentration of the drug, many hours are then required for its excretion. The intravenous use of the drug is contraindicated in patients with severe liver disorders, nephritis and severe uremia and it should be used with caution in cases of tuberculosis and hyperthyroidism. Caution must also be exercised in patients with any severe systemic disease. Preliminary liver and kidney function tests are advisable in suspected cases.

Dosage—Twenty cc of solution containing 15 Gm of neo iopax previously warmed to body temperature is injected intravenously, very slowly, into the cubital vein. Children are given correspondingly smaller doses.

Tests and Standards—

Neo-Iopax occurs as a white crystalline odorless powder, very soluble in water, insoluble in acetone benzene, chloroform ether and purified petroleum benzene. An aqueous solution is neutral to litmus.

Dissolve about 0.5 Gm of neo-iopax in 100 cc of water, add an excess of diluted hydrochloric acid, collect the liberated *N*-methyl-3,5-diiodo-4-pyridoxyl-2,6-dicarboxylic acid on a filter, wash and dry in a desiccator over sulfuric acid under a partial vacuum. It melts at

about 174 C., with decomposition heat the remainder of the resultant acid
 no
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 in

paper and divide into two portions to one portion add 1 cc of chloroform and 0.1 cc of ferric chloride solution no chloration is imparted to the chloroform layer (absence of free inorganic iodide) saturate the other portion with hydrogen sulfide no coloration or precipitation results (salts of heavy metals)

Dry about 1 Gm of neo-iopax, accurately weighed to constant weight at 100 C the loss in weight does not exceed 2 per cent Transfer about 1 Gm of neo-iopax, accurately weighed to a 500 cc Kjeldahl flask, and describe
 cation o
 ter 2, p.
 than 27
 dried su
 tared pl
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portions of sulfuric acid, respectively, ignite, cool and weigh as sodium sulfate the sodium found corresponds to not less than 9.2 per cent nor more than 9.4 per cent when calculated to the dried substance Transfer about 0.2 Gm of neo-iopax to a Parr sulfur bomb, determine the iodine content by the Lemp and Broderson Method (*Journal of the American Chemical Society* 39:2069) the amount of iodine found corresponds to not less than 51 per cent nor more than 53 per cent when calculated to the dried substance

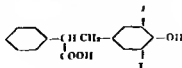
SCHIERING CORPORATION

Solution Neo-Iopax: 10 cc and 20 cc ampuls Each 1 cc contains 0.75 Gm of neo-iopax in sterile distilled water

Solution Neo-Iopax: 10 cc and 20 cc ampuls Each cc contains neo iopax 0.5 Gm, dissolved in sterile distilled water

U S patent 1,919,417 (July 25 1931, expires 1950) U S trade mark 297,925

PRIODAX. — β -(4-hydroxy-3,5-diiodophenyl)- α -phenyl-propionic acid — $\text{HO}(\text{C}_6\text{H}_4)_2\text{CH}_2\text{C}_6\text{H}_5(\text{CH})\text{COOH}$ — M W 494.1
 Priodax contains 51.38 per cent of iodine



Actions and Uses—Priodax is used as a medium for cholecystography. It is claimed to cause less nausea, vomiting and

acute
 may
 used,

Dosage—For intravenous urography, skiodan is administered in sterile aqueous solution (from 20 to 40 Gm in 100 cc.), the average dosage for adults being about 2 Gm for each 15 pounds of body weight; for retrograde pyelography an aqueous solution of skiodan (from 10 to 20 Gm in 100 cc) is injected through a ureteral catheter in the renal pelvis. Cystograms may be made with 3 to 5 per cent solutions. Aqueous solutions of skiodan should be kept protected from light, they can be kept for a considerable time without impairment but should be resterilized before use.

For retrograde pyelography, 10 to 20 Gm in 100 cc. skiodan solution is used. In thin patients, a 10 per cent concentration often suffices. The injection is made in the customary manner through the ureteral catheter. In cases of suspected stone, some urologists prefer a 5 per cent or 6 per cent solution for thin persons, to assure satisfactory contrast. In the preparation of skiodan solutions for retrograde pyelography, distilled water should be used. The solution should be sterilized by boiling or autoclaving.

On the day before the intravenous injection of skiodan the patient is given a soft diet, with a cleansing enema in the evening. During the night the fluid intake is restricted as much as possible.

Tests and Standards—

[illegible]

Dry about 1 Gm of skiodan, accurately weighed to constant weight at 100 C; the loss in weight does not exceed 1 per cent.

Transfer about 0.3 Gm of skiodan to a bomb tube, determine the iodine content by the Carius method the amount of iodine found corresponds to not less than 51.9 per cent nor more than 52.3 per cent when calculated to the dried substance. Weigh accurately about 0.3 Gm of skiodan in a tared platinum dish, add 5 cc. of sulfuric acid, gently heat while the fumes of iodine and sulfur trioxide are evolved, repeat twice, using two portions of 2 cc of sulfuric acid

each time cool and weigh as sodium sulfate the percentage of sodium corresponds to not less than 93 per cent nor more than 95 per cent calculated to the dried substance

WINTHROP CHEMICAL COMPANY, INC

Skiodan Powder 20 gram bottle

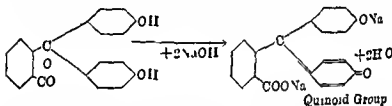
Sterile Solution Skiodan (40 per Cent by Volume)
50 cc bottles

Tablets Skiodan 1 Gm (for retrograde pyelography)

U S patent 1 842 626 (Jan 26 1932 exp res 1949) U S trade mark 283 045

Phenolphthalein Dyes

Phenolphthalein—long used by chemists as an indicator before its therapeutic properties were discovered—is a condensation product of phthalic anhydride and phenol. In neutral and acid



mediums it exists in a form in which there is no quinoid group but the presence of alkali ($pH = 8$ to 10) causes the characteristic rearrangement with typical salt formation and the presence of a quinoid group whereby the red color is formed.

This reaction is also characteristic of other members of the series. Phenolsulfonphthalein—also used as an indicator—contains an SO_3 group in place of the CO group in the phthalic anhydride nucleus. In phenoltetrachlorophthalein and phenoltetraiodophthalein the four hydrogen atoms in the benzene ring belonging to the phthalic acid nucleus have been replaced by chlorine and iodine respectively. In tetrabromophenolphthalein two bromine atoms are on each phenol group.

Actions and Uses—All of the compounds of the phenolphthalein type are used in medicine as diagnostic agents except phenolphthalein itself. Phenolphthalein is used for its cathartic action. Phenolsulfonphthalein and phenoltetrachlorophthalein are used because they pass unchanged through the body and at the same time have the property of intense color formation when the excretions are collected and alkalized. Bromsulfalein is used in a somewhat analogous way but instead of determining the amount excreted by the bile the amount (not excreted) in the blood gives an index of liver function. Tetrabromophenolphthalein and tetraiodophenolphthalein—which are employed in the form of the sodium salts—are used as carriers of bromine

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be more than 48 hours old). Meticulous roentgen ray technic is necessary, and if the interpretation of the cholecystogram is in question a check determination should be made either by the oral or, if preferred, by the intravenous method. The liver function test cannot be made by this method because the dye is not absorbed rapidly enough into the blood.

To make the test, 5 per cent solution of standard sodium phenetiothalein is collected one-half hour after intravenous injection of a drop of 5 per cent solution to a set of standard scales. Improved Method for Liver Function Test, J. F. [c] 1922) and modified by Cole, Copher and Graham (Simultaneous Cholecystography and Determination of Liver Function, J. A. M. A. 90:111 [April 7] 1928)

Tests and Standards.—

Phenetiothalein sodium occurs as bronze purple, odorless, slightly hygroscopic granules. It is soluble in water and alcohol.

permanent purple color appears

Intimately mix 0.1 Gm of the salt with 10 Gm of anhydrous sodium carbonate and heat to fusion, cool the mixture, dissolve in diluted hydrochloric acid and filter, add a few drops of hydrogen peroxide solution and agitate the mixture with a few cubic centimeters of chloroform; the chloroform layer is colored violet (iodine).

Transfer about 0.5 Gm, accurately weighed, of phenetiothalein sodium to a flat type weighing bottle and dry in a vacuum at 80 C to constant weight; the loss in weight is not more than 5 per cent.

Transfer about 0.2 Gm, accurately weighed, of phenetiothalein sodium to a bomb tube, determine the iodine by the Carious method; the amount of iodine found is not less than 56 per cent nor more than 59 per cent when calculated to the dry basis.

MALLINCKRODT CHEMICAL WORKS

Iso-Iodeikon (Granules): Bulk, Phenetiothalein Sodium

Iso-Iodeikon (Granules): 25 Gm ampuls

salt of tetraiodophenolphthalein. It contains not less than 85 per cent of tetraiodophenolphthalein. The separated tetraiodophenolphthalein contains not less than 60 per cent and not more than 63 per cent of I² U. S. P.

For description and standards see the U. S. Pharmacopeia under Iodophthalein Sodium.

Actions and Uses—Iodophthalein sodium is used for the roentgenologic examination of the gallbladder. Following the intravenous injection or if decomposition is avoided the oral administration the substance appears in the normal gallbladder in sufficient concentration to cast a shadow to the roentgen rays. After injection a few of the patients may have unpleasant sensations such as dizziness nausea various body pains and fall in blood pressure. The transitory fall in blood pressure may be relieved by the administration of from 0.5 to 1 cc of epinephrine hydrochloride solution (1 in 1000) intramuscularly. Iodophthalein sodium is useful as a diagnostic agent but workers are cautioned as to the selection of types of cases in which it is indicated and its possible toxicity in large doses. Myocardial insufficiency and uremia are considered contraindications and jaundice enjoins caution.

Dosage—To visualize the gallbladder in a patient weighing between 115 and 160 pounds (52 and 72.6 kg.) 3 Gm. of

avoid tissue necrosis. Breakfast is omitted. At noon a glass of milk is permitted and the evening meal is allowed as usual. Water by mouth is allowed at all times.

Iodophthalein sodium may be administered orally. 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each) or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice to be taken during and after the evening meal which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old). Keratin coated capsules may be used. Meticulous roentgen technic is necessary and if the interpretation of the cholecystogram is in question a control determination should be made either by the oral or if preferred by the intravenous method. Iodophthalein sodium is said to be preferable for intravenous injection.

ABBOTT LABORATORIES

Iodeikon Emulsion Powder Iodophthalein sodium 33.34 per cent in a vehicle composed of malt sugar 37.3 per cent powdered cocoa 18.3 per cent tartaric acid 8.25 per cent vanilla 2.2 per cent saccharine 0.54 per cent and menthol 0.07 per cent.

EASTMAN KODAK COMPANY

Tetraiodophenolphthalein Sodium Salt (Powder) Bulk

MALLINCKRODT CHEMICAL WORKS

Iodeikon (Powder) bulk

Iodeikon 35 Gm ampuls iodophthalein sodium

MERCK & Co, Inc

Iodophthalein Sodium (Powder) 35 Gm 25 Gm 100 Gm and 500 Gm bottles

Toxins for Immunity Tests

(See under Chapter XXI Serums and Vaccines, Diagnostic Agents)

Allergenic Extracts Diagnostic

(See under Chapter I Allergenic Preparations)

CHAPTER XIV

DIURETICS

Mercury Compounds

MERCUROPHYLLINE INJECTION — A sterile solution in water for injection of the sodium salt of *B* methoxy γ hydroxymercuri propylamide of trimethyl cyclopentane dicarboxylic acid ($C_{12}H_{17}NO_4HgNa$) (the mercuri compound) and of theophylline in approximately molecular proportions. It contains an amount of mercury equivalent to not less than 37 per cent and not more than 42 per cent of the labeled amount of the mercuri compound and not less than 93 per cent and not more than 107 per cent of the labeled amount of theophylline ($C_7H_8N_4O_2 \cdot H_2O$) "U S P"

For description and standards see the U S Pharmacopeia under Mercuriophylline Injection

Actions and Uses — Mercuriophylline injection is a potent diuretic. It is perhaps less toxic and more active than the purine free mercurial diuretics. It has been demonstrated that when theophylline is combined with the mercurial sloughs and venous thrombosis occur with less frequency and severity. Clinical experiments suggested that the presence of theophylline enhances the rate and completeness of absorption, so that the drug is effective and well tolerated by intramuscular as well as intravenous administration. Studies by a number of investigators give indication that mercuriophylline injection is an efficient diuretic. Supplementary administration of acidic salts such as ammonium chloride, tends to increase the diuresis.

Mercuriophylline injection is used to remove excess fluid in edema of congestive heart failure, nephrosis, and cirrhosis of the liver with

| | | | | | |
|---------------|---|---|---|---|---|
| nephritis and | . | . | . | . | . |
| restrict the | . | . | . | . | . |
| diuresis in | . | . | . | . | . |
| chloroemia | . | . | . | . | . |
| ammonium | . | . | . | . | . |
| depletion | . | . | . | . | . |

Dosage — Intramuscularly an amount equivalent to 0.1 Gm of the mercury compound and 40 mg of theophylline. Care should be taken to prevent leakage into the subcutaneous tissue. If it is desired to determine if the patient may have intolerance to the compound a much smaller dose should be injected for trial. Mercuriophylline injection is supplied in a concentration of 10 per cent (weight/volume) with respect to the sodium salt of the mercurated organic acid and 3.53 per cent with

respect to anhydrous theophylline. Each cubic centimeter of mercuriophylline injection represents 39 mg of mercury in non ionizable form.

When maximum diuresis is desired in patients with massive edema five tablets administered at one time will usually produce a response comparable to that obtained with injections. In severe cases reaccumulation of the dropsical fluid may be partly or entirely controlled with one or two tablets daily while in milder cases with occult edema one or two tablets three times daily, on two or three successive days is recommended for the relief of subjective symptoms of cardiac failure notably dyspnea. The diuretic effect may be enhanced by ammonium chloride, 5.85 to 7.8 Gm by mouth a day preceding administration of the tablets.

CAMERON PRODUCTS, INC.

Mercuripurin 1 cc and 2 cc ampuls

Mercuripurin Tablets Each enteric coated tablet contains a concentrate representing 0.74 cc of mercuriophylline injection U S P equivalent to 30 mg of mercury and 27 mg of anhydrous theophylline.

U S patent 2,117,901 (May 17, 1938 expires 1955) U S trade mark 315,683

MERSALYL AND THEOPHYLLINE—A mixture containing two parts by weight of mersalyl U S P and one part by weight of theophylline U S P.

Actions and Uses—(See under Mersalyl and Theophylline Injection)

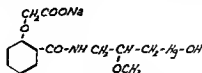
Dosage—Two tablets may be given in one dose in the morning after breakfast and repeated in four to five days if required. As an adjunct to intravenous medication one tablet may be given daily for one or two weeks but in such instances rest periods of one or two weeks should intervene between courses of treatment.

WINTHROP CHEMICAL COMPANY, INC.

Salyrgan-Theophylline Enteric Tablets Each tablet contains 80 mg mersalyl and 40 mg theophylline and is coated with shellac.

MERSALYL AND THEOPHYLLINE INJECTION
 —Mersalyl sterile solution in
 water for its by weight of
 mersalyl weight of theo-
 phylline -y (Hg) equiva-
 lent to not less than 39 mg of mercury more than 42 per

cent of the labeled amount of mersalyl, and not less than 93 per cent and not more than 107 per cent of the labeled amount of theophylline" U. S. P.



For description and standards see the U. S. Pharmacopeia under Mersalyl and Theophylline Injection

Actions and Uses—Mersalyl and theophylline injection has been demonstrated to produce less local reaction on intramuscular or intravenous injection than mersalyl alone and to be somewhat more effective. It is believed that the more rapid resorption of mersalyl in combination with theophylline accelerates diuresis and, by preventing the deposition of mercury, improves the local tolerance. Mersalyl and theophylline injection is proposed as a diuretic for dropsy in cardiorenal disease and in nephrosis, ascites of liver diseases and other conditions. It is contraindicated in acute nephritis and chronic kidney disease in an advanced stage with marked tubular and glomerular

eruptions When the use of mersalyl and theophylline injection is continued over a prolonged period of time the urine should be examined from time to time for albumin, casts and blood cells. Sudden fatalities have been reported following the use of mercurial diuretics and while these mishaps are rare compared to the number of times these drugs are used caution should be exercised. Since the available evidence is in favor of ventricular arrhythmia as the mechanism of these fatalities, especial precautions should be exercised in patients who already are candidates for such arrhythmia, for example, patients with frequent ventricular beats, heavily digitalized patients or those with recent myocardial infarction.

Dosage—For Adults Intramuscularly or intravenously mersalyl, 0.2 Gm and theophylline, 0.1 Gm. For susceptibility, test the patient with one half of the recommended dose. If well tolerated, the recommended dose may be given on the following day. In some cases this may have to be doubled for the full effect. Usually injections are not given more frequently than every three or four days. After relief of the dropsy, recurrences can often be prevented by occasional injections. For Children The above recommendations should be reduced by one half.

WINTHROP CHEMICAL COMPANY, INC.

Solution Salyrgan-Theophylline 1 cc and 2 cc ampuls
Each cubic centimeter contains mersalyl 0.1 Gm and theophylline 50 mg

U S patent 1 693 437 (Nov 27 1928 exp red) U S trademark 188 515

Urea

UREA—Carbamide— $\text{CH}_2\text{N}_2\text{O}$ —U S P

For description and standards see the U S Pharmacopeia under Urea

Actions and Uses—Urea is an active diuretic it is rapidly eliminated and is not poisonous It is useless in the treatment of tuberculosis and has no important solvent action on urinary calculi It may be employed when diuresis is indicated though it appears irrational in any renal disease characterized by retention of nitrogen Urea should not be used as a diuretic when there is impaired elimination Concentrated solutions of urea dissolve protein readily but have little action on healthy tissue hence urea has been used for the removal of necrotic tissue in infected wounds and for the removal of foul odors Certain observers believe that even weak solutions stimulate granulation and hasten the healing of wounds

Dosage—From 0.5 to 4 Gm Urea is given in solution or it may be enclosed in cachets

MALLINCHROFT CHEMICAL WORKS

Urea Pure Crystals bulk

MERCK & Co, INC

Urea (Crystals) bulk

Xanthine Derivatives

Structure and Relations—Caffeine theobromine and theophylline are methyl xanthines derived from xanthine by the introduction of two or three methyl radicals into a corresponding number of NH_2 groups As these may occupy various positions in the xanthine nucleus a considerable number of methyl xanthines exist naturally or by synthesis differing quantitatively in pharmacologic activity Those named however are the only ones of therapeutic importance namely caffeine (1 3 7 trimethylxanthine) theobromine (3 7 dimethylxanthine) and theophylline (1 3 dimethylxanthine)

Caffeine is usually obtained from tea or coffee theobromine is obtained from cacao or is made synthetically Theophylline

occurs in nature but in amounts too small to be commercially available. It is prepared synthetically. Theocin is a proprietary name for synthetic theophylline.

Actions and Uses—Theobromine and theophylline surpass caffeine in their diuretic, and perhaps in cardiac and muscular actions. They are, therefore, generally preferred in cardiac edemas, etc., since they are equally, or more, effective, more prompt and largely avoid the unpleasant side effects (insomnia, nervousness, gastric disturbance) which often interfere with the use of caffeine in adequate doses. This freedom from side effects holds true, particularly for theobromine. Theophylline surpasses theobromine in diuretic efficacy, but its action is probably not so lasting, it may produce gastric disturbances, renal irritation has been reported. Theobromine is, therefore, generally preferred, sometimes preceded for a few days by theophylline. If central stimulation is desired, caffeine must be used. In recent years the xanthine derivatives have been used but seldom as diuretics as a result of the introduction of the more effective mercurial diuretics.

Compounds—The slight solubility of theobromine and theophylline limits their usefulness. They are therefore used almost exclusively in the form of the readily soluble double salts (such as theobromine with sodium salicylate, U S P), which they form with a considerable number of compounds. There is no reason to suppose that the particular salt used to procure the solubility has any material influence on the action. The dosage of these added compounds is also generally too small to produce therapeutic effects. It may, therefore, be assumed that the various preparations which have been introduced are strictly equivalent.

Theobromine Compounds

THEOBROMINE AND SODIUM ACETATE—"A hydrated mixture of theobromine sodium ($C_7H_7N_3O_2Na$) and sodium acetate ($NaC_2H_3O_2$) in approximately molecular proportions. It yields not less than 55 per cent and not more than 65 per cent of theobromine ($C_7H_7N_3O_2$)."*U S P*

For description and standards see the *U S Pharmacopeia* under Theobromine and Sodium Acetate.

Actions and Uses—The uses of theobromine are similar to those of caffeine, but its action is said to be relatively greater on the heart and muscles and also as a diuretic. It does not act so powerfully on the central nervous system.

Theobromine is a weak diuretic, but its action is over which it is being well tolerated. Its power to sustain is not great.

Dosage—From 0.5 to 1 Gm, preferably in wafers or capsules. If in solution, this should be freshly prepared (with peppermint water), without sugar or mucilage.

THEOCALCIN.—A double salt or mixture of calcium theobromine ($[\text{C}_7\text{H}_7\text{O}_2\text{N}_4]_2\text{Ca}$) and calcium salicylate ($[\text{C}_7\text{H}_5\text{O}_3]_2\text{Ca}$). It contains not less than 44 per cent of theobromine.

Actions and Uses—Theocalcin acts like theobromine, over which it has the advantage of greater solubility. It is, however, less soluble than theobromine with sodium salicylate, on this account it is claimed to be less likely to produce gastric irritation.

Dosage—Average dose, from 0.5 to 1 Gm three times a day.

Tests and Standards—

Theocalcin is a white, amorphous powder having a saline taste. It is partly soluble in water.

An aqueous solution of theocalcin is alkaline to phenolphthalein. An aqueous solution of theocalcin (1 in 100) slightly acidulated with acetic acid becomes violet on the addition of ferric chloride solution. Transfer about 0.05 Gm of theocalcin to a test tube, add 3 cc of diluted acetic acid and heat to boiling, cool the contents of the test

thus obtained and it is more than 44 per cent of the weight of theocalcin taken. About 0.2 Gm of the precipitate obtained in the assay for theobromine volatilizers when slowly heated leaving only a negligible residue.

BILHUBER-KNOLL CORP

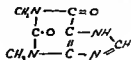
Theocalcin (Powder): bulk

Tablets Theocalcin: 0.5 Gm

U S patent 1547698 (July 28 1925 expired) U S trademark
194898

*Theophylline and Theophylline Compounds***THEOPHYLLINE—U S P—Theocin**

For description and standards see the U S Pharmacopeia under Theophylline and Theophylline Tablets



MERCK & CO., INC

Theophylline (*Powder*). 30 Gm, 124 Gm and 498 Gm bottles

WINTHROP CHEMICAL COMPANY, INC

Theocin (*Powder*): bulk Prepared synthetically

Preparation—

Theocin is obtained by heating the monoformyl derivative of 1,3-dimethyl 4,5-diamido 2,6-dioxy pyrimidin with alkalis resulting in the preliminary formation of an alkaline salt of the formyl compound. On further heating this splits off one molecule of water forming the alkali salt of theocin. Subsequent treatment with acids liberates theocin.

Tablets Theocin. 01 Gm

U S patent 716 994 (Dec 30 1902 expired) U S trademark 39,135

— **THEOPHYLLINE—U S P**
 — cent and not
 — $(\text{C}_7\text{H}_8\text{N}_4\text{O}_2)$
 — than 138 per
 — p

For description and standards see the U S Pharmacopeia under Theophylline Ethylenediamine Theophylline Ethylene diamine Injection and Theophylline Ethylenediamine Tablets

*Actions and Uses—*Theophylline ethylenediamine has the actions and uses of theophylline and theophylline with sodium acetate, over which it has the advantage of greater solubility. Like these it has a diuretic action and the xanthine derivatives are useful diuretics in congestive heart failure. There is apparently no satisfactory evidence to show that these drugs exert an immediate action which justifies their use in acute pulmonary congestion or edema, although they may be useful in preventing attacks by their diuretic effects. The xanthines stimulate the myocardium to increased vigor of contraction. This is accompanied by increased cardiac output and increased work of the heart. Clinical evaluation of the usefulness of the xanthines in the treatment of coronary artery disease is far from satisfactory and claims for such use do not appear accept

able in view of the existing evidence. Increased coronary blood flow produced by theophylline in the experimental animal follows, rather than precedes, the myocardial stimulation, and claims for the clinical use of this drug in increasing the blood supply to the heart are not acceptable until it can be shown that the increase in coronary flow is disproportionately large in comparison to the increase in cardiac metabolism. The xanthines are useful in the treatment of Cheyne Stokes respiration. At times the effect is transient but in other cases the effect may last several hours. Aminophylline is effective in the treatment of bronchial asthma, it finds its greatest field of usefulness in patients who are not relieved by epinephrine. It is probably a safer drug than epinephrine in occasional cases where there may be indecision concerning the "bronchial" or "cardiac" nature of asthmatic attacks. In general it is less effective than epinephrine and should not supplant the latter. There is no basis for claims that the xanthines effectively reduce high blood pressure. The available evidence is opposed to claims that these drugs are useful in the treatment of peripheral vascular disease.

Dosage—Orally, from 0.1 to 0.2 Gm. three times daily may be necessary but it is pointed out that this high dosage is warranted only in exceptional cases, by rectal administration in the form of suppositories, or, as a retention enema, intramuscularly, 0.48 Gm., intravenously 0.24 Gm. to 0.48 Gm. When given intravenously, infusion should be performed slowly in order to avoid untoward effects.

AMERICAN PHARMACEUTICAL CO., INC.

Tablets Aminophylline 0.1 Gm. and 0.195 Gm.

Tablets Aminophylline 0.2 Gm. enteric coated. The enteric coating consists of shellac.

BARLOW-MANEY LABORATORIES, INC.

Tablets Aminophylline 0.1 Gm. and 0.2 Gm. enteric coated. The enteric coating consists of a mixture of myristic acid, opal wax, castor oil, cholesterol and sodium taurocholate.

ERNST BISCHOFF COMPANY, INC.

Aminophyllin (Powder) bulk

Tablets Aminophyllin 0.1 Gm.

Solution Aminophylline Ampuls 0.24 Gm. in 10 cc. and 0.48 Gm. in 2 cc.

BRISTOL LABORATORIES, INC.

Solution Aminophylline Ampuls 0.48 Gm. in 2 cc. and 0.24 Gm. in 10 cc.

H. L. DUBIN LABORATORIES, INC.

Solution Aminophyllin Ampuls 0.24 Gm in 10 cc 0.48 Gm in 2 cc and 0.48 Gm in 20 cc

Suppositories Aminophyllin 0.36 Gm

Tablets Aminophyllin 0.1 Gm 0.2 Gm and 0.2 Gm (enteric coated)

INDO PRODUCTS, INC.

Tablets Aminophyllin 0.1 Gm

Solution Aminophylline with Benzyl Alcohol 2%, Ampuls 0.48 Gm in 2 cc and 0.24 Gm in 10 cc

GANT AND INGRAM, INC.

Aminophylline (Powder) bulk

LAKESIDE LABORATORIES, INC.

Solution Aminophylline Ampuls 0.48 Gm in 2 cc 0.24 Gm in 10 cc and 0.48 Gm in 20 cc

Tablets Aminophylline 0.1 Gm and 0.2 Gm and 0.2 Gm enteric coated

Tablets Aminophylline 0.1 Gm

LEDERLE LABORATORIES, INC.

Solution Aminophylline Ampuls 0.25 Gm in 10 cc and 0.50 Gm in 2 cc

Tablets Aminophylline 0.1 Gm and 0.2 Gm

MERCK & CO., INC.

Theophylline Ethylenediamine (Powder) 30 Gm 124 Gm and 498 Gm bottles

THE W. W. S. MERRILL CO. LOESER LABORATORY DIVISION

Solution Aminophylline Ampul 0.48 Gm in 2 cc and 0.24 Gm in 10 cc

Aminophylline Tablets 0.1 Gm

F. S. MILLER LABORATORIES, INC.

Theophylline Ethylenediamine Injection 2.4% W/V 10 cc and 20 cc ampuls

Solution Aminophylline 2.4% W/V in Ethylenediamine Solution 1% V/V (with Benzyl Alcohol 2% V/V) 2 cc ampuls

Tablets Theophylline Ethylenediamine 90 mg and 180 mg

PHARMEDIC CORPORATION

Aminophylline (*Powder*): bulk

Solution Aminophylline: Ampuls 0.24 Gm in 10 cc and 0.48 Gm in 2 cc

Suppositories Aminophylline: 0.36 Gm

Tablets Aminophylline: 0.1 Gm

G. D. SEARLE & Co

Aminophyllin (*Powder*): bulk

Solution Aminophyllin: Ampuls 0.25 Gm in 10 cc and 0.5 Gm in 20 cc for intravenous injection, ampuls 0.5 Gm in 2 cc with benzyl alcohol, 40 mg in sufficient distilled water to make 2 cc, for intravenous injection

Tablets Aminophyllin: 0.1 Gm and 0.2 Gm and 0.1 Gm and 0.2 Gm enteric coated. The enteric coating consists of a mixture of mastic and magnesium stearate

SMITH-DORSEY COMPANY

Solution Aminophylline: Ampuls 0.5 Gm in 20 cc, 0.25 Gm in 10 cc and 0.5 Gm in 2 cc

Tablets Aminophyllin: 0.1 Gm and 0.2 Gm

WILLIAM R. WANNEN & Co, INC.

Solution Aminophylline: 0.24 Gm in 10 cc ampuls

Tablets Aminophyllin: 0.1 Gm

WARREN-TELO PRODUCTS COMPANY

Tablets Aminophylline: 0.1 Gm

THEOPHYLLINE AND SODIUM ACETATE —

U. S. P.—Theocin Soluble—"Yields not less than 55 per cent and not more than 65 per cent of anhydrous theophylline ($C_7H_8N_4O_2$)" U. S. P.

For description and standards see the U. S. Pharmacopeia under Theophylline and Sodium Acetate and Theophylline and Sodium Acetate Tablets

Dosage—From 0.2 to 0.35 Gm, best given after meals

WINTHROP CHEMICAL COMPANY, INC.

Theocin Soluble (*Powder*): bulk

Tablets Theocin Soluble: 0.16 Gm

U. S. patent 716,994 (Dec. 30, 1902, expired) U. S. trademark 39,135

CHAPTER XV

ECBOLICS

Ergot, the dried sclerotium of *Claviceps purpurea* developed on rye, contains a number of specific alkaloids to which it owes its therapeutic effects. In addition a great variety of chemical substances have been isolated from the crude drug. These include carbohydrates, lipoids, dyes, amino acids and a number of biogenous amines. Of the last group may be mentioned histamine, tyramine and acetylcholine substances which are pharmacologically active but which play a negligible role in the therapeutic effect of the drug.

The alkaloids thus far isolated consist of several pairs of optical isomers, one member of each pair being pharmacologically potent and the other member almost inert. The members of each pair may be interconverted by chemical procedures, and it has been suggested that the inert alkaloids may be formed to some extent from the active ones in the process of extraction.

The isomeric pairs of alkaloids may be listed as follows:

| Potent | Relatively Inactive | Formula |
|----------------|---------------------|---------------------|
| 1 Ergotoxine | Ergotinine | $C_{26}H_{40}O_8Na$ |
| | ψErgotinine | |
| 2 Ergotamine | Ergotaminine | $C_{26}H_{40}O_8Na$ |
| 3 Ergosine | Ergosinine | $C_{26}H_{40}O_8Na$ |
| 4 Ergocristine | Ergocristinine | $C_{26}H_{40}O_8Na$ |
| 5 Ergonovine | Ergometrinine | $C_{26}H_{40}O_8Na$ |

It may be noted that the first of the five groups consists of three rather than of two members and furthermore that the members of each other pair are interconvertible. Ergonovine is the inert alkaloid, while ergotamine, ergotaminine, ergosine, ergocristine, and ergometrinine are the active members of the pairs.

Various molecular complexes consisting of a potent and an inert alkaloid have also been isolated. These may show a pharmacologic activity somewhat different from the average of those of its components. In this group may be mentioned sensibamine (ergotamine plus ergotaminine) and ergoclavine (ergosine plus ergosinine).

Common to all these alkaloids is the presence of the ergoline nucleus (ergoline, ergoline acid, (Ergomonatin, ergot, and the ergoline group). Isomerism in the ergoline acid part of the molecule is believed to account for differences in members of the same pair. The various pairs of alkaloids differ in the other products of hydrolysis which are unique in the field of alkaloidal chemistry in that certain of them are

been employed. Of this group, the colorimetric method which utilizes the blue coloration produced by *p* dimethylaminobenzaldehyde with the alkaloids and dependent on the indole group of the lysergic acid component, has been extensively used. Such methods do not distinguish between ergonovine and the ergotoxine ergotamine group, and consequently are not a true measure of the pharmacologic potency unless a constant proportion of these groups in various ergots could be assumed. To overcome this difficulty, assays involving a previous separation of the two groups have been proposed. The Broom Clark method, which is based on the inhibition of the action of epinephrine on the isolated rabbit uterus, does not assay ergonovine, which lacks this particular action.

ERGOT—Ergot of Rye — *Secale Cornutum* P. I. — "The dried sclerotium of *Claviceps purpurea* (Fries) Tulasne (Fam. *Hypocreaceae*), developed on rye plants.

"The potency of Ergot shall be such that when assayed as directed 1 Gm. shall be equivalent to not less than 0.5 milligram of the U. S. P. Ergotoxine Ethanedisulfonate Reference Standard." U. S. P.

For description and standards see the U. S. Pharmacopeia under Ergot and Fluidextract of Ergot.

Actions and Uses—The several active principles of ergot have actions that differ somewhat, and the combined effect is utilized in ergot. The action of histamine and tyramine in ergot is probably negligible, and only the alkaloids exert a prolonged effect on the human uterus when ergot is used clinically.

Ergot causes powerful tonic, sometimes tetanic, contractions of the uterus. It also produces contractions of other involuntary muscles such as those of the blood vessels, bladder, stomach and intestines. Extreme and long continued contraction of the blood vessels, especially of those of the extremities, may lead to gangrene.

The principal use of ergot is to prevent postpartum hemorrhage. For as the secretion is given until it should be asphyxia or

"after-pains." Ergot is also used for hemorrhage from the uterus in menorrhagia and metrorrhagia. Its use for hemorrhage from other internal organs is not rational.

Ergot has also been employed in a number of other conditions, in which, however, it is not recommended. These include congestions in various regions, early stage of acute pneumonia, pulmonary congestion, in typhoid fever, diabetes insipidus, colliquative night sweats due to relaxation of the blood vessels and circulatory failure.

Dosage—2 Gm It is sometimes administered in the form of powder, but most commonly in the form of fluidextract

ERGOT ASEPTIC—A liquid extract of ergot standardized by the cockscomb method of assay to have the same potency as fluidextract of ergot U S P

Actions and Uses—The same as those of ergot

Dosage—1 to 2 cc Ergot aseptic is intended for intramuscular injection Ergot aseptic is marketed in ampules only The date of manufacture appears on each package and the product is not guaranteed to possess its full potency for more than one year from time of manufacture

Preparation—

Ergot is extracted with diluted alcohol acidulated with hydrochloric acid The percolate is partially neutralized with alkali and concentrated by distillation in a partial vacuum at a temperature not above 80 C A large excess of alcohol is added to the concentrated percolate and the material which precipitates is removed The liquid portion is freed from alcohol by distillation in a partial vacuum at a low temperature and chlorobutanol in the proportion of 0.005 Gm per cc added to the aqueous slightly acid liquid After three weeks the liquid is assayed adjusted to proper volume and sealed in ampules The finished ampules are tested for sterility and potency

Ergot aseptic is standardized to the same potency as fluidextract of ergot U S P, as determined by the cockscomb method described in the U S P

PARKE, DAVIS & COMPANY

Ampoule Ergot Aseptic. 1 cc

ERGOTAMINE TARTRATE C₁₇H₁₉N₃O₆

—The tartrate
For descrip
under Ergotam

Actions and Uses—Ergotamine tartrate stimulates the motor nerve endings of the cerebral cortex of the autonomic nervous system. It produces a tonic contraction of the uterus and a spasmolytic action on the smooth muscle of the gastrointestinal tract. It also produces a tonic contraction of the blood vessels of the skin and a spasmolytic action on the smooth muscle of the blood vessels of the internal organs.

action of ergot and in toxic doses causes gangrene and convulsions There is evidence that ergotamine tartrate is of value in many cases of migraine The drug is not always a prophylactic and its continued administration will not always prevent attacks Caution in its use is advisable on account of the danger of poisoning from long continued use or overdosage

Ergotamine tartrate is proposed for use when the action of ergot to produce uterine contraction is desired, it is contraindicated whenever tonic contraction of the uterus would be dangerous Ergotamine tartrate is also stated to be indicated in

amino acids. These groups undoubtedly determine the variations in pharmacologic action shown by the active alkaloids of different pairs, e. g. ergotoxine and ergonovine.

Ergotoxine may be crystallized from benzene, carbon bisulfide and acetone. It is insoluble in water and light petroleum sparingly soluble in ether, and very soluble in methyl and ethyl alcohol, chloroform, acetone and ethyl acetate. The phosphate of ergotoxine is soluble in 313 parts of water at room temperature, the ethanesulfonate is sparingly soluble in water, somewhat more soluble in ethyl alcohol and dissolves readily in methyl alcohol. Ergotamine is insoluble in water, sparingly soluble in ethyl alcohol and very readily soluble in chloroform.

Ergotamine crystallizes from ethyl alcohol and benzene, more soluble than ergotoxine. It is readily soluble in nitrobenzene, pyridine and dilute sodium hydroxide. It forms a tartrate, a phosphate and a bitartrate, all of which are water soluble. Ergotamine is soluble in chloroform and in pyridine. It is much less soluble than ergotamine in other solvents from which it crystallizes relatively solvent free, unlike most of the ergot alkaloids which tend to retain solvent of crystallization.

Ergonovine may be crystallized from a number of solvents, possibly most readily from benzene and chloroform. In contrast to the other alkaloids it is appreciably soluble in water and comparatively insoluble in chloroform. It forms many crystalline salts which are markedly soluble in water. Ergonovine is more basic than the other alkaloids and less readily precipitated by Mayer's reagent. It is present in aqueous and alcoholic extracts of those ergots which contain it, unlike ergotoxine and ergotamine which are extracted by alcohol but not by water. The content of ergonovine is not constant in specimens of ergot from different localities and may even vary in specimens from the same locality. It occurs in lower concentrations (up to 0.2 mg. per Gm. of ergot) than does the ergotoxine-ergotamine group which may reach 2 mg. per Gm. of ergot. Ergometrine is even more basic than ergonovine, much more soluble in chloroform, only slightly soluble in water and may be crystallized from acetone. It forms crystalline salts, unlike the other alkaloids of the inert series.

Pharmacology—Ergotoxine, ergotamine, ergosine and presumably ergocristine show essentially the same type of pharmacologic action although certain individual variations have been observed.

They cause a moderate and prolonged increase in tone and rhythmic contractions of the uterus. The blood pressure is increased through peripheral stimulation of the motor sympathetic mechanism and also a parafysis of this mechanism is produced so that the effect of epinephrine on the blood pressure is lessened or reversed. The inhibition of epinephrine action

by ergot alkaloids may also be demonstrated on other smooth muscle organs more readily on those to which the sympathetic nerve supply is predominantly motor, such as the rabbit uterus. In sufficient dosage they cause cyanosis of the cockscomb and with toxic doses gangrene through vascular occlusion. Gangrene may also appear clinically on administration of toxic doses. The vascular effects of these alkaloids vary considerably both in animals and in man. Poisonous doses in the intact animal produce acute manifestations essentially due to central action consisting of excitement, tremor, weakness, pyrexia, vomiting, convulsions, and certain signs of sympathetic stimulation.

Ergotoxine shows slightly greater activity than ergotamine in inhibiting the action of epinephrine on isolated tissues. Ergosine is probably even more potent than ergotoxine in this regard. Ergotamine is only about two thirds as toxic to white mice as ergotoxine and the latter alkaloid is at least twice as effective on body temperature as ergotamine. Small doses causing a fall and larger doses a rise in temperature by action on the central nervous system.

Ergonovine is effective on the uterus in smaller doses and concentrations than are the other alkaloids. This difference is particularly apparent in the puerperal state when the uterus is especially sensitive to ergonovine. The uterine action is the only appreciable effect of moderate doses of ergonovine, unpleasant side actions being rarely encountered clinically. The promptness of the uterine action in comparison with that produced by ergotoxine and ergotamine, is an outstanding clinical feature, also it is much more effective when administered by mouth than are the latter alkaloids. It increases both the tone and the rate and amplitude of rhythmic contractions of the uterus, the latter effects probably being proportionately greater than the tonus changes. The duration of effect although probably less than that of ergotoxine and ergotamine is at least comparable with that of these alkaloids. The circulatory effects which are referable to actions on the central nervous system and peripheral vascular mechanism vary with the animal and with dose.

It shows definitely less tendency to produce gangrene than ergotoxine and ergotamine. It is less toxic than these two alkaloids, but in poisonous doses produces similar effects.

Assay—All ergot preparations especially those containing water, deteriorate with age. It is necessary therefore to standardize them and the date of assay should be indicated on the container.

Ergot is assayed officially in this country by the cockscomb method (see U. S. P. XII), which measures the total pharmacologically active alkaloids. Various physical and chemical methods which measure the total alkaloidal content have also

been employed. Of this group the colorimetric method which utilizes the blue coloration produced by *p*-dimethylaminobenzaldehyde with the alkaloids and dependent on the indole group of the lysergic acid component has been extensively used. Such methods do not distinguish between ergonovine and the ergotoxine ergotamine group and consequently are not a true measure of the pharmacologic potency unless a constant proportion of these groups in various ergots could be assumed. To overcome this difficulty assays involving a previous separation of the two groups have been proposed. The Broom-Clark method which is based on the inhibition of the action of epinephrine on the isolated rabbit uterus does not assay ergonovine which lacks this particular action.

ERGOT—Ergot of Rye —*Secale Cornutum* P I — The dried sclerotium of *Claviceps purpurea* (Fries) Tulasne (Fam *Hypocreaceae*) developed on rye plants

The potency of Ergot shall be such that when assayed as directed 1 Gm shall be equivalent to not less than 0.5 milligram of the U S P Ergotoxine Ethanesulfonate Reference Standard U S P

For description and standards see the U S Pharmacopeia under Ergot and Fluidextract of Ergot

Actions and Uses—The several active principles of ergot have actions that differ somewhat and the combined effect is utilized in ergot. The action of histamine and tyramine in ergot is probably negligible and only the alkaloids exert a prolonged effect on the human uterus when ergot is used clinically.

Ergot causes powerful tonic sometimes tetanic contractions of the uterus. It also produces contractions of other involuntary muscles such as those of the blood vessels, bladder, stomach and intestines. Extreme and long continued contraction of the blood vessels especially of those of the extremities may lead to gangrene.

The principal use of ergot is to prevent postpartum hemorrhage. For this purpose a full dose is sometimes given as soon as the second stage of labor terminates but it should not be given until the placenta has been expelled. Its use during labor should be avoided as it may cause rupture of the uterus or asphyxia of the child. It is employed as a prophylactic for after pains. Ergot is also used for hemorrhage from the uterus in menorrhagia and metrorrhagia. Its use for hemorrhage from other internal organs is not rational.

Ergot has also been employed in a number of other conditions in congestive pulmonary and circulatory failure. These include acute pneumonia, insipidus colic, and blood vessels.

Dosage—2 Gm It is sometimes administered in the form of powder, but most commonly in the form of fluidextract

ERGOT ASEPTIC—A liquid extract of ergot, standardized by the cockscornb method of assay to have the same potency as fluidextract of ergot U S P

Actions and Uses—The same as those of ergot

Dosage—1 to 2 cc Ergot aseptic is intended for intramuscular injection Ergot aseptic is marketed in ampules only The date of manufacture appears on each package and the product is not guaranteed to possess its full potency for more than one year from time of manufacture

Preparation—

Ergot is extracted with diluted alcohol acidulated with hydrochloric acid The percolate is partially neutralized with alkali and concentrated by distillation in a partial vacuum at a temperature not above 80 C and free percola to the assay final

Ergot aseptic is standardized to the same potency as fluidextract of ergot U S P, as determined by the cockscornb method described in the U S P

PARKE, DAVIS & COMPANY

Ampoule Ergot Aseptic: 1 cc

ERGOTAMINE TARTRATE— $(C_{23}H_{25}N_2O_9) \cdot H_2C_4H_4O_6$

—The tartrate of an alkaloid obtained from ergot U S P For description and standards see the U S Pharmacopeia under Ergotamine Tartrate and Ergotamine Tartrate Tablets

Actions and Uses—Ergotamine tartrate stimulates the motor

action of ergot and in toxic doses causes gangrene and convulsions There is evidence that ergotamine tartrate is of value in many cases of migraine The drug is not always a prophylactic and its continued administration will not always prevent attacks Caution in its use is advisable on account of the danger of poisoning from long continued use or overdosage

Ergotamine tartrate is proposed for use when the action of ergot to produce uterine contraction is desired, it is contraindicated whenever tonic contraction of the uterus would be dangerous Ergotamine tartrate is also stated to be indicated in

hemorrhage following abortion, after curettage and in post partum endometritis. It is also used by some physicians in conditions in which there is believed to be overactivity of the sympathetic nervous system, but its value here is not established.

Dosage — Intramuscularly, the average dose is 0.25 mg., orally, 1 mg. two to four times daily. Caution should be exercised in the repeated use of ergotamine, cases of gangrene have been reported where the use of the alkaloid has been continued over a period of some days. For migraine the dose recommended is 0.25 mg. by subcutaneous injection to be followed in two or three hours by a full dose of 0.5 mg. if no untoward effects have been seen or if the original dose has not been effective. If preferred two or three tablets containing 1 mg. each may be given sublingually or by ingestion to be repeated hourly up to 8 or 9 tablets but this method of administration is not so effective as when the drug is given by the subcutaneous route.

SANDOZ CHEMICAL WORKS, INC.

Solution Gynergen ampuls 0.5 cc and 1 cc. Each cc contains 0.5 mg. of ergotamine tartrate and a small excess of tartaric acid, 15 cc and 100 cc bottles. Each cc contains 1 mg. of ergotamine tartrate and a small excess of tartaric acid.

Tablets Gynergen 1 mg.

U. S. patent 1,394,233 (Oct. 18, 1921, exp. red.) 1,435,187 (Nov. 14, 1922, expired) U. S. trademark 173,047

CHAPTER XVI

GASTROINTESTINAL DRUGS

Antacids

ALUMINUM HYDROXIDE GEL-N N R—An aqueous suspension containing not less than 3 per cent nor more than 42 per cent of aluminum oxide chiefly in the form of aluminum hydroxide. Flavoring, sweetening and preservatives may be added.

See also standards of the U S Pharmacopeia under *Gelatinum Aluminii Hydroxidum*.

Actions and Uses—Aluminum hydroxide gel has been shown to be an effective gastric antacid neutralizing hydrochloric acid of the stomach by chemical reaction. It does not increase the pH of the gastric juice beyond the point which interferes with peptic digestion, does not stimulate a compensatory increase in free gastric acidity and does not produce systemic alkalization which are the principal disadvantages of ordinary alkalis. The amphoteric nature of aluminum hydroxide gel is of not of clinical significance because it reacts as an acid only in fluids with a pH above 9 such a pH is not encountered in the gastrointestinal tract. Its so called buffer action occurs only at a pH of about 4. It is presumed that the acid salt aluminum chloride which is formed by the reaction of aluminum hydroxide with hydrochloric acid in the stomach is reconverted to the original compound or other aluminum compounds by reaction with the less acid contents of the small intestine and the chloride is reabsorbed. Its mild astringent and demulcent properties are believed to be of some importance in the local effect on peptic ulcer. Some evidence also suggests that its effectiveness may be further explained by the tendency to increase mucin secretion and the ability to precipitate pepsin *in vitro*.

As with other aluminum compounds aluminum hydroxide is not absorbed from the gastrointestinal tract to any appreciable extent and is therefore nontoxic when administered orally. Its astringent property may produce a constipating effect.

There is evidence available to suggest that administration of aluminum compounds may interfere with the absorption of certain minerals and can produce a phosphorus deficiency in the presence of a relative or absolute pancreatic deficiency diarrhea or low phosphorus diet by combination with phosphates in the intestinal tract. This objection does not affect its usefulness in uncomplicated peptic ulcer and gastric hyperacidity, since the diet employed in these conditions is ordinarily relatively rich in phosphorus. Aluminum hydroxide gel may possess adsorptive properties but specific conclusive evi-

dence that acid, toxins, bacteria or gases are absorbed is lacking, and in the case of hydrochloric acid is opposed by in vitro evidence to demonstrate that its reaction with this substance is completely accounted for on the basis of simple chemical neutralization.

Aluminum hydroxide gel is recognized for oral use as an adjunct in the treatment of peptic ulcer (gastric and duodenal) to promote healing, relieve pain and control hemorrhage in this condition and for the control of gastric hyperacidity when this can be recognized as a cause of distress. Its oral or rectal use in the treatment of other gastrointestinal conditions is not adequately supported by existing clinical evidence.

Dosage—Aluminum hydroxide gel is administered orally in doses of from 4 to 8 cc in one half glass of water or milk every two or four hours or one half to one hour after meals. It may be administered by the method of continuous drip by stomach tube in dilutions of 1 part to 2 or 3 parts of water (25 to 33½ per cent aluminum hydroxide gel) at the rate of 15 to 20 drops a minute for a total of approximately 1500 cc of diluted suspension per twenty four hours.

Tests and Standards—

Aluminum hydroxide gel occurs as a white or light gray suspension which may settle out to some extent or form a semisolid on standing but which liquefies on shaking. The specific gravity at 25 C is from 1.030 to 1.042.

| | |
|---|----------------|
| Transfer about 5 Gm of aluminum hydroxide gel to a glass container and add 10 cc of diluted hydrochloric acid. The solution is clear and colorless. | excess ammonia |
| water | about |
| ammonia | 1 cc. of |
| 5 Gm | distilled |
| sodium | |
| red lit | |

Dissolve 10 Gm of aluminum hydroxide gel in 10 cc of diluted hydrochloric acid and boil. Cool dilute to 250 cc and filter if necessary. To 10 cc add 1 cc of barium chloride solution and allow to stand for ten minutes. The turbidity is not greater than that produced by 0.2 cc of fiftieth normal sulfuric acid in 10 cc of water.

The pH at 25 C of aluminum hydroxide gel is between 6.4 and 7.2. Dissolve 2.5 Gm of the gel in 5 cc of diluted sulfuric acid and boil. The solution meets the U S P XI test for arsenic. Dissolve 10 Gm of aluminum hydroxide gel in 10 cc of diluted sulfuric acid. The resultant solution conforms to the U S P XI test for heavy metals.

Transfer 25 Gm of aluminum hydroxide gel, accurately weighed to an Erlenmeyer flask add 25 cc of distilled water and 0.2 cc of potassium chromate solution. Titrate with tenth normal silver nitrate to a faint pink color. The chloride content is not greater than 0.35 per cent.

Transfer about 3 Gm of aluminum hydroxide gel, accurately weighed to an Erlenmeyer flask dilute to 30 cc and maintain at 37.5 C. Titrate with tenth normal hydrochloric acid during forty minutes, adding the acid in 0.5 cc portions toward the end of the titration using bromophenol blue as indicator. The volume of tenth normal acid used is not more than 2.500 cc, nor less than 1.250 cc per hundred Gm.

Transfer about 3 Gm of aluminum hydroxide gel accurately weighed to a 250 cc beaker and dilute to 100 cc. Add 10 cc of diluted hydrochloric acid heat to boiling and make the mixture alkaline to methyl red with ammonia water. Dilute to 200 cc heat to boiling and wash

four times by decantation. Filter and wash the precipitate free of chlorides with an aqueous solution containing 1 part of ammonia water in 25 parts of solution. Dry the precipitate and ignite at 900 C to constant weight. The aluminum oxide content is not less than 3 nor more than 4.2 per cent.

BARLOW MANEY LABORATORIES

Aluminum Hydroxide Gel 480 cc bottles. Contains the equivalent of 3.6 to 4.4 per cent of aluminum oxide (U. S. P. XII).

MACALLISTER LABORATORY

Aluminum Hydroxide Gel 480 cc and 384 liter bottles. Contains 4.6 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide) with saccharin sodium U. S. P. and oil of peppermint U. S. P. as flavoring agents.

SCHIEFFELIN & CO

Aluminum Hydroxide Gel Contains 5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide). Saccharin and Oil of Peppermint U. S. P. are added as flavoring agents. Marketed in bottles of 480 cc and 384 liters.

L. R. SQUIBB & SONS

Aluminum Hydroxide Gel 360 cc and 3840 cc bottles. Contains the equivalent of 3.6 to 4.4 per cent of aluminum oxide (U. S. P. XII).

THE UPJOHN COMPANY

Aluminum Hydroxide Gel 240 cc and 3840 cc bottles. Contains the equivalent of 3.6 to 4.4 per cent of aluminum oxide (U. S. P. XII).

WINTHROP CHEMICAL COMPANY, INC

Creamalin Contains 5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide). Oil of peppermint is added as a flavoring agent. Marketed in bottles of 180, 240, 360 and 480 cc.

Creamalin (Unflavored) Contains 5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide). Marketed in bottles of 180 cc and 480 cc.

ALUMINUM PHOSPHATE GEL—An aqueous suspension containing not less than 3.8 per cent nor more than 4.2 per cent of aluminum phosphate (AlPO_4). Flavoring, sweetening and preservatives may be added.

Actions and Uses—Aluminum phosphate gel has antacid astringent and demulcent properties analogous to those of aluminum hydroxide gel but will not interfere with phosphate absorption. Because the acid combining power of aluminum phosphate gel is less than one half that of aluminum hydroxide gel of the same concentration, it is necessary to prescribe it in amounts more than twice as great. Indications for the selection of aluminum phosphate gel would include cases of ulcer in which a high phosphate diet could not be continuously maintained or which were accompanied by a relative or absolute deficiency of pancreatic juice or by diarrhea. The available, somewhat inconclusive evidence indicates that aluminum phosphate gel gives as good results as aluminum hydroxide gel in the treatment of peptic ulcer when it is employed in sufficient amounts.

Dosage—Fifteen to 30 cc alone or with water or milk may be administered every two hours during the active stage of the ulcer. Later the dose may be reduced to 45 cc four times daily (with or after each meal and at bedtime) or to 30 cc six times daily (with or after and between meals and at bedtime).

Tests and Standards—

Aluminum phosphate gel occurs as a white odorless suspension which may settle out to some extent on standing. Its specific gravity at 25 C is from 1.032 to 1.044. The *pH* at 25 C of aluminum phosphate gel is between 6.0 and 7.2.

Dilute 1 Gm of aluminum phosphate gel to 100 cc and mix. To 5 cc of the diluted gel add 1 cc of sodium hydroxide solution. 1 cc of 1 per cent alcoholic alizarin sulfonate solution and neutralize with 36 per

| | | |
|--------------|-----------|-----|
| 5 cc of | acid | and |
| 2 cc of | appears | |
| which | colorless | |
| solution | Gm of | |
| aluminum | ates the | |
| <i>pH</i> of | | |

Transfer 5 Gm of aluminum phosphate gel to a glass container, add 10 cc of diluted a clear and colorless add 8 cc of ammonium is insoluble in excess solution.

Dissolve 10 Gm of aluminum phosphate gel in 10 cc of diluted hydrochloric acid and boil. Cool, dilute to 250 cc and filter if necessary. To 10 cc add 1 cc of barium chloride solution and allow to stand for ten minutes; the turbidity is not greater than that produced by 0.2 cc of fiftieth normal sulfuric acid in 10 cc of water. Dissolve 25 Gm of the gel in 5 cc of diluted sulfuric acid and boil; the solution meets the U S P test for arsenic. Dissolve 10 Gm of aluminum phosphate gel in 10 cc of diluted sulfuric acid; the resultant solution conforms to the U S P test for heavy metals.

Transfer 25 cc of aluminum phosphate gel to a beaker, add 5 cc

nitric acid and 20 cc of ammonium molybdate solution. Digest on the steam bath for one hour, filter and wash the precipitate with 2 per cent nitric acid solution followed by washing with 1 per cent potassium

nitrate solution. Transfer about 20 cc of the filtrate to a 100 cc volumetric flask, add nitric acid until solution is complete and dilute to the mark. Mix thoroughly, transfer 10 cc to a 400 cc beaker dilute to 100 cc, warm to 80 C, add an excess of ammonium molybdate solution and digest on the steam bath for one hour. Filter and wash the precipitate with 2 per cent nitric acid followed by 1 per cent potassium nitrate solution until the filtrate is no longer acid. Dissolve the precipitate in one-half normal sodium hydroxide and titrate with one-half normal acid using phenolphthalein as the indicator. Each cubic centimeter of one-half normal sodium hydroxide is equivalent to 2.654 mg of AlPO_4 . The calculated aluminum phosphate content is no less than 3.8 nor more than 4.2 per cent.

WYPTH, INCORPORATED

Phosphaljel—480 cc bottle. Aluminum phosphate gel containing 4 per cent of aluminum phosphate, 5 per cent of glycerin, not more than 0.5 per cent of sodium benzoate as a preservative and oil of peppermint as a flavoring agent.

TRIBASIC CALCIUM PHOSPHATE—Precipitated calcium phosphate—After ignition to a constant weight contains an amount of phosphate (PO_4) corresponding to not less than 90 per cent of $\text{Ca}_3(\text{PO}_4)_2$. —U. S. P.

For description and standards see the U. S. Pharmacopoeia under Tribasic Calcium Phosphate.

Actions and Uses—It neutralizes the hydrochloric acid of the gastric juice by chemical action. It possesses a sorptive power and causes systemic alkalization. It has been claimed that tribasic calcium phosphate is somewhat constipating. It has been shown that some of the calcium is absorbed, hence this salt may be used to obtain the therapeutic effects of calcium.

Dosage—From 1 to 5 Gm.

MAGNESIUM TRISILICATE—Contains not less than 20 per cent of magnesium oxide (MgO) and not less than 45 per cent of silicon dioxide (SiO_2). —U. S. P.

For description and standards see the U. S. Pharmacopoeia under Magnesium Trisilicate and Magnesium Trisilicate Tablets.

Actions and Uses—It neutralizes the hydrochloric acid of the gastric juice by chemical action. It possesses a sorptive power

erties but it does not interfere with peptic digestion nor does it usually induce alkalosis. It is nontoxic in ordinary amounts, but large doses sometimes induce diarrhea because of the magnesium chloride formed. It is used for the relief of gastric hyperacidity and pain in gastric and duodenal ulcer.

Dosage—From 1 to 4 Gm before meals or food taken at other times, the single dose and the frequency of repetition depending on the degree of acidity and the relief afforded.

TRIBASIC MAGNESIUM PHOSPHATE—When ignited to constant weight contains not less than 98 per cent of $Mg_3(PO_4)_2 \cdot 5H_2O$.

For description and standards see the U. S. Pharmacopeia under Tribasic Magnesium Phosphate.

Actions and Uses—Tribasic magnesium phosphate has been proposed for use as an antacid. It has the advantage over alkaline hydroxides such as magnesium hydroxide and alkali carbonates such as sodium bicarbonate in that being soluble it neutralizes the excess of acid in the stomach but does not produce systemic alkalization. It has been claimed that tribasic magnesium phosphate has a laxative action.

Dosage—From 1 to 5 Gm.

Emollients

GASTRIC MUCIN—The fraction precipitated by approximately 60 per cent alcohol from the supernatant liquid after pepsin hydrochloric acid digestion of hog stomach linings.

Actions and Uses—Gastric mucin is prepared for use in the treatment of peptic ulcers.

Dosage—Average dose 25 Gm which can be given at two hour intervals.

Tests and Standards—

Gastric mucin occurs as a white to yellow powder or brownish yellow granules. It possesses a slightly salty taste and characteristic odor of peptones. Both forms yield a viscous gray opalescent solution when triturated with water.

Dry approximately 1 Gm of gastric mucin accurately weighed to constant weight at 100 C; the loss in weight does not exceed 6 per cent.

Incinerate approximately 1 Gm of gastric mucin accurately weighed in a muffle furnace at 500 C; the ash content does not exceed 6.5 per cent.

lenmeyer
ethanol
density
density of
combined
vaporate
mercury
volume
not less

Determine the nitrogen content in the dried alcohol insoluble residue (described in the foregoing paragraph) by the Kjeldahl method according to Methods of Analysis of the Association of Official Agricultural Chemists ed 4 page 23 the nitrogen content is not less than 7.0 nor more than 9.0 per cent

Transfer 0.1 Gm of the dried alcohol insoluble residue as previously obtained to a 125 cc Erlenmeyer flask and add 50 cc of two normal sulfuric acid solution. Boil for 1 hour. Cool. Add 10 cc of 10% sodium carbonate and 25 Gm of sodium potassium tartrate is dissolved in

Preparation
of mucin
screen,
at 25 C
viscosity
10 cc is

is not below 1.30 nor above 3.50

Gastric mucin is manufactured by license from the Gastric Mucin Committee of Northwestern University Medical School under U S patent 1 829 270 (Oct 27, 1931, expires 1948)

THE ARMOUR LABORATORIES

Gastric Mucin (*Granules*) 226.8 Gm and 453.6 Gm packages

Gastric Mucin (*Powder*) 226.8 Gm and 453.6 Gm packages

FREDERICK STEARNS & COMPANY DIVISION

Gastric Mucin (*Granules*) 5 Gm packages and 226.8 Gm packages

Gastric Mucin (*Powder*) 226.8 Gm and 453.6 Gm packages

WILSON LABORATORIES

Gastric Mucin (*Granules*) 226.8 Gm packages

Gastric Mucin (*Powder*) 453.6 Gm packages

MAGMA OF BISMUTH—'Magma of Bismuth contains bismuth hydroxide and bismuth subcarbonate in suspension in water and yields not less than 5.2 per cent and not more than 5.8 per cent of Bi_2O_3 .' N F

For description and standards see The National Formulary under Magma of Bismuth

Dosage—From 4 to 15 cc every two or three hours

I. J. HART & COMPANY, INC.

Lac Bismo Magma of Bismuth

U S trademark 57250

SHARP & DOHME, INC.

Cremo Bismuth Milk of Bismuth N F VII

U S trademark 29335

Laxatives

AGAR—Agar Agar—The dried mucilaginous substance extracted from *Gelidium corneum* (Hudson) Lamouroux and other species of *Gelidium* (fam. *Gelidiaceae*) and closely related algae (Class *Rhodophyceae*). Agar contains not more than 1 per cent of foreign organic matter, and yields not more than 1 per cent of acid insoluble ash and not more than 20 per cent of moisture when determined by the toluene method IX. U S P

For description and standards see the U S Pharmacopeia under Agar

MERCK & CO., INC.

Agar Agar (Flakes and Powder) Bulk

REMARKS—A mixture containing about 50 per cent

Actions and Uses—Metamucil is intended as an adjunct in the treatment of constipation. It encourages elimination by the formation of a soft plastic water retaining gelatinous residue in the lower bowel. The muciloid is also claimed to have a demulcent effect in the presence of inflamed mucosa. Metamucil has been mixed with barium sulfate to obtain more uniform dispersion of the barium for x ray visualization.

Dosage—Four to 7 Gm one to three times daily each dose thoroughly stirred in a glass of water and followed by an additional glass of liquid. Children receive proportionate amounts.

according to weight and age. It is important that adequate fluids be ingested to assure a soft bulk. Metamucil should not be used carelessly so that a state of dependency is reached.

Tests and Standards—

Metamucil is a white to cream colored slightly granular powder possessing little or no odor and a slightly acid taste. A uniform suspension is formed when 10 Gm of the powder is stirred rapidly into 250 cc of water. As the hydration and swelling of the mucilaginous portion progresses, the mixture assumes a soft gelatinous consistency.

Place about 10 Gm of metamucil in a dry 25 cc glass stoppered graduate. Fill the graduate to the 25 cc mark with a solution made by mixing 27 cc of chloroform and 73 cc of carbon tetrachloride. Stopper the graduate and mix the contents thoroughly. Set the graduate aside and observe the contents at the end of two hours. A light colored layer appears at the bottom of the tube approximately equal in volume to a brownish colored layer which appears at the top of the tube. Mechanically separate the layers formed in the graduate and dry the material at 80°C. Powder from the lower layer is soluble in water and responds to tests for dextrose, powder from the upper layer forms a mucilage with water and is microscopically identical with fragmented material obtained from the outer epidermis of blonde psyllium seed (*Plantago ovata* Forsk).

Transfer 50 Gm of metamucil to a suitable flask and determine the moisture content by means of the method for moisture by toluene distillation described in the U. S. P. XII the moisture content found is not more than 4 per cent.

Transfer exactly 20 Gm of metamucil to a 150 cc beaker add 0.1 Gm of decolorizing charcoal and 30 cc of 80 per cent, v/v ethyl alcohol preheated to 65-70°C. Stir the mixture thoroughly for three minutes and filter while still warm into a 50 cc volumetric flask. Rinse the beaker twice with 7 to 9 cc of warm 80 per cent alcohol and filter the rinsings through the residue on the filter paper, adding the washings directly to the volumetric flask. Cool to 25°C add three drops of stronger ammonia water fill to the mark with 80 per cent alcohol and mix the contents of the flask. Allow the mixture to stand for ten minutes and then determine the optical rotation of a portion of the solution in a 2 decimeter tube using sodium light. Multiply the observed angular rotation by 21.7 to obtain the percentage of anhydrous dextrose present in the specimen taken the amount of dextrose found is not less than 46 per cent nor more than 50 per cent.

G. D. SEARLE & CO.

Metamucil • 113 Gm 227 Gm and 454 Gm containers.

U. S. patent 2,095,259 (Oct. 12, 1937 expires 1954) U. S. patent 2,132,484 (Oct. 11, 1938 expires 1955) U. S. trademark 117,704 (Oct. 2, 1934)

LIQUID PETROLATUM—Liquid Paraffin.—White Mineral Oil.—Heavy Liquid Petrolatum.—“A mixture of liquid hydrocarbons obtained from petroleum.” U. S. P.

For description and standards see the U. S. Pharmacopoeia under Liquid Petrolatum and Emulsion of Liquid Petrolatum, and the National Formulary under Emulsion of Liquid Petrolatum with Phenolphthalein.

Actions, Uses and Dosage—See Useful Drugs.

PETROGALAR LABORATORIES INC

Petrogalar Liquid petrolatum 65 cc emulsified with 0.4 Gm agar agar in a menstruum containing glycerin acacia saccharin flavoring benzoic acid and water to make 100 cc. Contains sodium benzoate 0.06 per cent as preservative.

Alkaline Petrogalar Petrogalar with magnesia magma 8 cc per 100 cc. No saccharin or preservative.

Cascara Petrogalar Petrogalar with non bitter fluid extract of cascara sagrada 13.2 cc per 100 cc and sodium benzoate 0.07 per cent as preservative.

Phenolphthalein Petrogalar Petrogalar with phenolphthalein 0.32 Gm. Contains 0.06 per cent as preservative.

Unsweetened Petrogalar Petrogalar with saccharin omitted. Contains sodium benzoate 0.06 per cent as preservative.

U. S. trademark 165 616

SMITH DORSEY COMPANY

Emulsion Liquid Petrolatum Chocolate Flavored
A palatable emulsion containing 60 per cent (by volume) of liquid petrolatum 1 per cent agar agar per 30 cc and 0.1 per cent of benzoic acid.

Emulsion Liquid Petrolatum with 0.1 Gm Phenolphthalein Chocolate Flavored

Emulsion Liquid Petrolatum with 0.3 Gm Phenolphthalein Chocolate Flavored

SMITH OIL & REFINING COMPANY

Mineral Oil bulk

F. R. SQUINN & SONS

Mineral Oil 180 cc 480 cc and 960 cc bottles

Mineral Oil Emulsion Mineral oil 50 cc agar 0.75 Gm karaya 0.75 Gm sodium benzoate 0.1 Gm acacia glycerin water and flavoring sufficient to make 100 cc.

Mineral Oil Emulsion and Phenolphthalein Mineral oil emulsion with 0.31 Gm phenolphthalein per 100 cc.

U. S. patent 1 799 804 (April 7 1931 expires 1948) and 1 913 561 (June 13 1933 expires 1940)

PETROLATUM — Petroleum Jelly — A purified semi solid mixture of hydrocarbons obtained from petroleum.
U. S. P.

For description and standards see the U. S. Pharmacopoeia under Petrolatum.

SARGENT'S DRUG STORE

Petrobran Each 100 Gm contains petrolatum 74 Gm
bran 22 Gm with powdered licorice and 'oil of pineapple
(ethyl butyrate) sufficient to flavor

PLANTAGO SEED—Psyllium Seed—Plantain Seed—

The cleaned dried ripe seed of *Plantago Psyllium* Linne or
of *Plantago arenaria* Waldstein et Kitaibel (*P. ramosa* [Gilib]
Aschers) known in commerce as Spanish or French Psyllium
Seed or of *Plantago ovata* Forskal known in commerce as
Blonde Psyllium or Indian Plantago Seed (Fam *Plantaginaceae*)

Plantago Seed contains all of its natural mucilage and not
more than 0.5 per cent of foreign organic matter. It yields
not more than 4 per cent of total ash and not more than 1 per
cent of acid insoluble ash. *N F*

For description and standards see the National Formulary
under Plantago Seed

Actions and Uses—Plantago seed by virtue of its indigesti-
bility and mucilaginous character acts as a mild laxative. The
addition of ground plantago seed to the food of rats and dogs
has been found to be followed by darkening of the kidneys
and when prolonged its use was followed by the appearance of
microscopic pigment granules in the tubules of rats. The sig-
nificance of this has not been determined.

Dosage—From 4 to 15 Gm one to three times a day.
Plantago seed may be mixed with orange juice or prune juice
and eaten without mastication or the dose may be mixed with
a little hot water and the resulting gelatinous mass spread on
bread or taken with other food.

SCHIEFFELIN & Co

Psyllium Seed bulk

CHAPTER XVII

HEMATICS

Iron and Iron Compounds

Iron is used in medicine (1) in the form of metallic or elementary iron (reduced iron, U S P), (2) in the ferrous or unoxidized form of combination—responding to tests for ferrous ions (ferrous carbonate in mass of ferrous carbonate

in syrup of ferrous form, the ferric compounds (ferric chloride in the form of complex

compounds of iron

Complex (masked or nonionic) iron compounds are those compounds of iron whose solutions do not respond to the ordinary tests for ferrous or ferric ions because in them the iron is part of a radical. Complex compounds of iron do not have the astringent taste of simple iron solutions. The permanence of these complex radicals differs widely, while some, such as soluble ferric phosphate, N F, and solution of peptonized iron, N F, are converted to simple ionic iron by action of dilute acids, others resist treatment with strong acids or with alkalis. The complex iron compounds occurring naturally in animal and vegetable tissues (which are often termed food irons) belong generally to the more resistant class, while the complex iron compounds produced artificially are as a rule decomposed rather readily. There is, however, no sharp line of distinction between the natural complex iron compounds and those products artificially produced, nor is there any good evidence that they differ in therapeutic action. Until a difference in their effects has been demonstrated we may class together all complex iron compounds whose solutions are not decomposed into simple ionic iron by digestion at body temperature with 0.2 per cent hydrochloric acid and pepsin (It should be emphasized that salts of iron which give the iron test directly are classed as inorganic iron, whatever their acid radicals may be, and that true iron albuminate and iron peptonate are inorganic iron compounds).

Actions and Uses.—Solutions of ferric iron are used externally as styptics. Tincture of ferric chloride is an astringent and is used in applications to the skin. The principal action is on the surface of the skin and on the mucous membrane. For this purpose, ferric salts, as ferric chloride, are preferred. They are hence used to stop bleeding and to disturb the growth of bacteria when dissolved in water. provided the fluid is

to permit solution. So far as the complex iron compounds are not decomposed by gastric digestion, they also are devoid of gastric effects, but, on the other hand, it has been claimed that certain hemoglobin like compounds escape absorption altogether. Bunge supposed that only "organic iron" could be absorbed and assimilated by the body, the reputed action of inorganic iron being altogether indirect and due to its local effect on the alimentary canal. This theory was modified by Abderhalden to the effect that inorganic iron while it could not be converted into hemoglobin, nevertheless stimulated the conversion of "organic iron." Later work (Tartakowski), however, proves that inorganic iron is absorbed and it is in the form of a complex iron compound that it is shown that ferrous iron aids recovery from the anemia of repeated hemorrhages.

Starkenstein (Heffner-Heubner Handbuch der experimentelle Pharmakologie) reports that Reiman has shown that ferrous salts are effective in bringing about a reticulocyte response, hemoglobin and red blood cell increase in much smaller amounts than the ferric salts, 100 mg of iron as ferrous salts daily were shown to be effective. A difference exists between the different iron preparations in their local irritant and astringent action, which is absent in most of the complex iron compounds. These local actions may be desirable in some cases and undesirable in others. This should mainly determine the selection of the particular iron preparation most suitable for each patient. Suitable diet (especially liver, kidney, meat and spinach) is sometimes more effective than the iron preparations presumably by the cooperation of other factors, for in pernicious anemia liver extract that is practically iron free is equally active.

Simple Iron Salts

FERROUS LACTATE—*Ferri Lactas*—Iron Lactate—*Ferrum Lacticum*— $\text{Fe}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 3\text{H}_2\text{O}$ —The ferrous salt of lactic acid. The salt contains approximately 19 per cent of metallic iron.

Actions and Uses—Ferrous lactate is a mild chalybeate, which, because of its feeble taste, may be taken without difficulty.

Dosage—From 60 mg to 1.3 Gm. Owing to its liability to oxidation it is best prescribed in solutions containing much sugar. Syrup dissolves 1 Gm in 120 Gm.

Tests and Standards—

Ferrous lactate occurs in pale greenish white crusts consisting of small needle shaped crystals or transparent green scales, having a slight, peculiar odor and a sweetish ferruginous taste. It is slowly soluble in about 40 parts of cold and in 12 parts of boiling water, almost insoluble in alcohol, freely soluble in a solution of an alkali citrate, yielding a green solution. When strongly heated the salt froths gives out dense white acid fumes, chars and finally leaves a brownish red residue.

The aqueous solution of the salt has a greenish yellow color and a slightly acid reaction, and gives a deep blue precipitate with potassium ferricyanide, and a light blue one with potassium ferrocyanide. A 2 per cent aqueous solution of the salt should not yield more than a faint opalescence with a lead acetate solution (*limit of absence of sulfate, chloride, citrate tartrate and malate*). The aqueous solution after acidulation with hydrochloric acid should not yield any precipitate or coloration when treated with hydrogen sulfide (*foreign metals*). The aqueous solution, acidulated with nitric acid, should not afford more than slight opalescence with barium chloride solution or with silver nitrate solution (*limit of sulfate or chloride*). If 25 cc. of a 2 per cent aqueous solution of the salt is mixed with 5 cc. of diluted sulfuric acid, the mixture boiled for a few minutes, an excess of sodium hydroxide solution added and the mixture filtered, the filtrate when mixed with a few drops of alkaline cupric tartrate solution and boiled does not yield a red precipitate (*sugar*). If a portion of the salt is triturated with sulfuric acid, no offensive odor is developed (*butyric acid*), nor is any gas evolved (*carbonate*) and the mixture, after standing for some time does not assume a brown color (*sugar, gum or other readily carbonizable impurities*). If from 1 to 1.5 Gm. of the salt is weighed and moistened with nitric acid and carefully ignited in a porcelain crucible it leaves a residue of ferric oxide weighing not less than 27 per cent nor more than 27.8 per cent of the material taken this residue does not have an alkaline reaction on litmus paper, nor yield anything soluble to water (*foreign salts*).

Complex Iron Salts

IRON AND AMMONIUM CITRATES—"Contains ferric citrate equivalent to not less than 165 per cent and not more than 185 per cent of Fe"—U S P.

For description and standards see the U S Pharmacopeia under Iron and Ammonium Citrates and Iron and Ammonium Citrate Capsules

Actions and Uses—See preceding article, Iron and Iron Compounds. Iron and ammonium citrates is a hematinic which is practically nonastringent.

Dosage—1 Gm

Pentnucleotide

PENTNUCLEOTIDE—The sodium salts of the pentose nucleotides from the ribonucleic acid of yeast. Pentnucleotide is prepared from yeast nucleic acid by hydrolysis for twenty four hours with 1 per cent sodium hydroxide solution. The lead salts prepared from the acidified hydrolyzed solution are decomposed with hydrogen sulfide and the liberated acids are concentrated and precipitated with alcohol. The sodium salts are prepared by neutralization with sodium hydroxide. The final product is approximately an 8 per cent solution of the sodium salts of what appear to be four nucleotides, the solution has a *pH* of 7.2 and is preserved with cresol, U S P, 0.3 per cent.

Actions and Uses—Pentnucleotide is indicated in infectious conditions accompanied by leukopenia or neutropenia such as agranulocytosis (agranulocytic angina, malignant neutropenia, pernicious leukopenia).

It is now recognized that the vast majority of these conditions follow the use of chemotherapeutic agents and aminopyrine, acetanilid, dinitrophenol and cinchophen have been repeatedly incriminated. More recently it has been shown that extreme leukopenia occasionally developing into a complete agranulocytosis is one of the most common of the severe toxic reactions caused by sulfonamide therapy.

With a total white count below 2500 pentnucleotide should be used immediately when the differential count shows a significant reduction in polymorphonuclear neutrophils and when aleukemic leukemia and aplastic anemia have been excluded.

Dosage—The contents of one vial (10 cc) pentnucleotide should be injected undiluted into the gluteal muscle four times daily. The recommended four vials (40 cc daily) should be continued until the temperature has fallen and an increase appears not only in the total white blood cell count but also in the percentage of polymorphonuclear neutrophils. In favorable cases this usually occurs in from two to five days after the initiation of treatment. In some cases myelocytes and young polymorphonuclears may appear as early as 36 hours after beginning pentnucleotide but lack of improvement in the blood picture in four or five days is not necessarily an indication that a favorable clinical result will not eventually occur. If there has been no response at the end of 10 days further therapy with pentnucleotide is probably useless.

After a favorable response to intensive treatment (40 cc daily) has been obtained one vial (10 cc) should be administered once or twice daily until the white blood cell count has been normal for several days. Intensive treatment must be resumed if the white blood cell count falls again.

Although reactions such as dyspnea, precordial distress, bradycardia, sweating or vomiting occasionally a sharp chill or febrile reaction immediate or delayed have been reported they occur infrequently and are seldom severe when pentnucleotide is given intramuscularly. If these reactions should occur, they may be minimized by administering the drug in small divided doses into an anesthetized site.

Tests and Standards—

1. To 10 cc of the ammoniacal filtrate add 5 cc. of 10 per cent calcium chloride solution. A gelatinous precipitate forms. Filter and wash with water. Add 1 cc. of diluted nitric acid to the precipitate, wash with 2 cc. of water, to the

solution (10 per cent) and again evaporate to dryness a purplish to rosy or brownish red coloration forms (*guanidine*). To 10 cc. of the ammoniacal filtrate add 5 cc. of 10 per cent calcium chloride solution. A gelatinous precipitate forms. Filter and wash with water. Add 1 cc. of diluted nitric acid to the precipitate, wash with 2 cc. of water, to the

dissolved precipitate add 0.5 cc ammonium molybdate solution a yellow coloration and a yellow precipitate forms on gentle warming (phosphates)

Treat 5 cc of pentnucleotide with 5 cc. of a solution of brucine acetate (10 per cent), a white precipitate forms, becoming crystalline on standing

solution (10
0.1 cc of 1
coloration is
solution no
pentnucleotide

volume of freshly prepared hydrogen sulphide water, treat according to U S P test for heavy metals no more color change is shown than when 5 cc of pentnucleotide is treated with 1 cc of diluted hydrochloric acid and an equal volume of water To 5 cc of pentnucleotide add several drops of silver nitrate solution (10 per cent) a white precipitate forms which dissolves on shaking the mixture

To 5 cc of pentnucleotide add 10 cc of lead acetate solution and 0.2 cc of glacial acetic acid a white precipitate forms Agitate the mixture for one or two minutes and filter with suction, wash the precipitate well with water, suspend in 15 cc of distilled water, and treat with excess hydrogen sulphide, stir well and filter into a tared flat shallow weighing dish, evaporate nearly to dryness on the steam bath, add about 5 cc. of dehydrated alcohol, evaporate the alcohol then dry

dissolve
phenolph
hydroxid
tenths no
stance
add 5 c
weight
0.45 Gm

SMITH, KLINE & FRENCH LABORATORIES

Vials Pentnucleotide: 10 cc

U S trademark 301 527

Fibrin Ferments and Thromboplastic Substances

The clotting of blood (that is, the transformation of the fibrinogen of circulating blood into the insoluble fibrin of blood clot) has been shown to be due to the action of the fibrin ferment (thrombin) on the fibrinogen of the blood The fibrin ferment of thrombin exists in the blood in the form of its fore factor on by the calcium salts calcium salts, however factor may be furnished or blood platelets or by injured tissues It has been designated as "zymoplastic" substance by Schmidt, as "thrombokinas" by Morawitz, and as "thromboplastic substance" or "thromboplastin" by Howell

It is generally agreed that in the conversion of inactive pro thrombin to active thrombin both thromboplastic substance and calcium ions are concerned, but the precise nature of the reaction is undetermined It is variously interpreted in the different theories of coagulation that have been proposed

The chemical nature of thromboplastic substance is also a matter of controversy. This material is readily extracted from fresh or dried tissues by aqueous solutions, and from dried or dehydrated tissues by the action of alcohol, ether or other lipid solvents. The aqueous extracts contain protein and are much more potent than those obtained with lipid solvents. It is characteristic of both kinds of extracts that their thromboplastic action undergoes a gradual deterioration when kept exposed to air. In the extracts made with alcohol, ether, etc., the active component was formerly believed to be lecithin, but Howell Gratia and Levene and others have shown that purified lecithin is devoid of thromboplastic activity. On the other hand cephalin as usually prepared has marked thromboplastic properties, and the general view has been that this thromboplastic substance present in the tissues and blood platelets is a water soluble protein cephalin compound or complex. Such a compound has however, not been isolated in a condition of chemical purity and the real nature of thromboplastin is still a subject for investigation, although it seems probable that it is a combination of some kind, between a protein and a phospholipid.

Actions and Uses—Preparations containing thromboplastin are said to be useful when applied locally in the treatment of hemorrhage, especially hemorrhage from oozing surfaces, like wise in the treatment of scar tissues, in nosebleed, and in surgery of the bones, glands nose and throat, but many surgeons have abandoned their use even for such purposes. Intravenous injection is probably dangerous, and there is no satisfactory evidence that subcutaneous injection is useful. Preparations should be standardized by testing specimens of blood *in vitro* and should reduce the coagulation time significantly. They should be proved to be sterile. The Council holds that there is no evidence to warrant the internal use of these substances and further that such use, on account of the danger from anaphylaxis from preparations containing animal proteins, is likely to be harmful unless proper precautions are taken. There appears to be no evidence that this danger is connected with local applications, but even before such use physicians should inquire into the patient's history to determine whether or not sensitivity to these proteins exists.

BRAIN LIPOID—Impure Cephalin—Impure Kephalin.—An extract of the brain of the ox, or other mammal, prepared according to the method of Howell as applied in practice by Hirschfelder (*Lancet* 2:542, 1915) and described below.

Actions and Uses—See preceding article Fibrin Ferments and Thromboplastic Substances.

Dosage—Brain lipid may be spread on gauze sponges, on pledgets, or on the tissues themselves, or an emulsion may be prepared by shaking up with physiological solution or sodium chloride and used in the same way or sponged over the tissues.

For use in an office or dispensary, a 5 per cent ethereal solution of brain lipid suffices and can be kept ready for use for some time (several months) in a sterile dropper bottle from which an opalescent emulsion can be prepared extemporaneously by dropping from 10 to 30 drops into an ounce of physiological solution of sodium chloride and then shaking. This solution can also be dispensed by pharmacists provided the opening in the stopper of the dropper bottle is kept slightly open to prevent the ether's blowing off when the bottle is shaken or heated.

Tests and Standards—

Brain lipid (impure cephalin) is prepared from ox brain which is run through a hashing machine, then covered with 3 volumes of alcohol and agitated two or three times. The excess of alcohol is then poured off and squeezed out gently through linen, care being taken to avoid great force in wringing out the alcohol as this tends to break up the brain tissue into very finely divided particles which pass through the filter. The residue is then covered with 3 volumes of ether shaken vigorously and filtered first through cotton and then through filter paper. The clear filtrate thus obtained is evaporated to dryness over a water bath leaving a yellow residue of fatty appearance and consistency. (This residue consists largely of cephalin but though the latter is not in the pure state it is extremely active in accelerating the clotting of blood *in vitro*.)

The method of preparation renders it sterile. It can be transferred on a sterile spatula or knife blade to sterile vessels. It retains its activities for several weeks.

(The impurities largely the lecithins and myelins do not materially interfere with the activity of the cephalin but on the contrary facilitate its emulsification in physiological solution of sodium chloride and thus facilitate its intimate miscibility with blood.)

SOLUTION BRAIN EXTRACT—Liquor Extracti Cerebri—Solution Thromboplastin Hess—An extract of cattle brain in physiological solution of sodium chloride prepared by the method of Hess (*J A M A* 66 558 [Feb 19] 1916 foot note 2)

*Actions and Uses—*See preceding article Fibrin Ferments and Thromboplastic Substances

*Dosage—*The solution may be applied directly to the bleeding tissues or sprayed on them or a sponge or tampon may be immersed in it and then pressed on the bleeding surface.

Preparation—

Cattle brains are obtained fresh from the slaughter house stripped of their membranes washed in running water and weighed. They are then passed through a meat chopping machine three times and to the quantity prepared an equal quantity of physiological solution of sodium chloride is added. This suspension is allowed to remain in the refrigerator for forty eight hours and is then pressed through cheese cloth twice. To tissue solution of sodium chloride is added in the proportion of 15 parts of tissue to 1 part of solution of sodium chloride. The solution is then filtered through cheese cloth and is ready for use. (The solution is not a permanent preparation.)

LEDERLE LABORATORIES, INC.**Thromboplastin Local: 20 cc vials****Tests—**

The potency of thromboplastin local Lederle is tested as follows: Transfer 0.5 cc of oxalated blood plasma (0.1 per cent oxalate) to each of a series of tubes, and add 0.2 cc of thromboplastin local Lederle to each tube. Also transfer 0.5 cc of oxalated blood plasma to each of a control series of tubes and add 0.2 cc of physiologic solution of sodium chloride. To each tube (and control) add 0.2 cc of calcium chloride solution the strength of which is determined by control tests as follows: that dilution of calcium chloride (usually 0.15, 0.25 or 0.5 per cent) is chosen with which the plasma forms solid clots in not less than 20 minutes. Thromboplastin local Lederle must cause clotting of the oxalated blood (such as to permit complete inversion of the tubes) within one minute; the controls must fail to show clotting at the expiration of 20 minutes.

E. R. SQUINN & SONS**Thromboplastin Local: 20 cc vials****Tests—**

Blood plasma is obtained by bleeding 45 cc of sheep's blood into a tube containing 5 cc of 1 per cent sodium oxalate in physiological solution of sodium chloride, centrifuging the mixture to obtain the clear plasma and preserving this at a low temperature. A 0.5 per cent

without loss of its contents.

Liver and Stomach Preparations

Whole liver extracts of liver and dried stomach stimulate maturation of erythrocytes in pernicious anemia and in certain other macrocytic anemias. The council has accepted only those preparations of liver or stomach which are primarily intended for the treatment of pernicious anemia.

The daily ingestion of 200 to 400 grams of whole liver is effective in inducing a remission in pernicious anemia and in maintaining a normal red blood cell count. Concentrates for oral administration are made from such amounts of liver, but these have lost a certain amount of the original activity of the liver from which they are derived. Extracts suitable for parenteral administration may be prepared from 10 to 15 Gm of liver and these possess a therapeutic potency equal to that of the larger amounts of liver given by mouth. Similar effects can be produced by 30 to 40 Gm of desiccated stomach and by combinations of stomach tissue and liver.

For liver extracts and for preparations of stomach the minimum dose is 1 U. S. P. unit per day, or in the case of intramuscular liver preparations multiples of this at longer intervals.

(e. g. 7 units per week) A U S P unit is the minimum amount which, when given daily to a suitable patient with pernicious anemia in relapse, will cause an adequate hematopoietic response. Inasmuch as material derived from about thirty times as much liver must be given by mouth to produce the same response as when given by injection it has been necessary to define the "unit" either as an "oral unit" or as an "injectable" unit according to the method of administration of each preparation. For the purpose of standardization (not as a plan to be followed routinely in the treatment of patients) the material is given daily with proper hematopoietic checks to at least three patients whose red blood cell counts are determined before treatment is started, on the day that it is started and on the seventh day and the fourteenth day of treatment. Daily reticulocyte counts are made during the complete period of the "reticulocyte response." These data are submitted by the manufacturer to the Anti Anemia Preparations Advisory Board of the United States Pharmacopeia which evaluates them and assigns unitage. The board has ruled that at present a strength greater than 15 units per cubic centimeter will not be assigned to a preparation because of the possibility of loss during the concentration process, of unknown factors of value in the treatment of patients with pernicious anemia.

In assigning units to preparations of liver extract or other anti anemia preparations, the following points are considered by the board in connection with other available data from therapeutic tests conducted in the manner specified:

- 1 The character and degree of the reticulocyte response
- 2 Rate of increase of red blood cells
- 3 Clinical factors modifying these responses
- 4 Efficiency of the method of manufacture in preserving the potency of the product
- 5 The following figures are especially useful to the board in assigning unitage

| Initial Red Blood Cell
Count (Millions per
Cubic Millimeter) | Peak of
Reticulocyte Curve
(per Cent) |
|--|---|
| 10 | 41 |
| 15 | 38 |
| 20 | 18 |
| 25 | 11 |
| 50 | 5 |

These figures are not to be considered as "standards" inasmuch as modifying factors in each individual patient, may change the degree of the response. Under the normal for every patient the ideal test patient should

Actions and Uses—Extralim is proposed for use in the oral treatment of pernicious anemia. See preceding article Liver and Stomach Preparations.

Dosage—For cases of pernicious anemia in relapse, an initial dosage of 2 Gm (four pulvules) three times daily is suggested. 15 Gm (three pulvules) three times daily constitutes an adequate maintenance dose for most cases. The amount necessary for maintenance varies with different individuals and can be determined only after repeated examinations.

Preparation—

An extract of mammalian livers (point approximately coagulate protein filtrate is reduced admixed with finely minced fresh hog stomachs or fresh hog stomach linings. The hydrogen ion concentration is adjusted to approximately pH 5 and the mixture allowed to react or digest for about two hours at 37.5 C. It is then spread out in a thin layer on pans and dried under vacuum. The dried product is removed from the drier and ground, then extracted with petroleum ether to remove fat. This is dried under vacuum and ground to the proper fineness. The proportions used are such that there is represented in the finished product two to four parts of original liver to one part of original stomach tissue material.

LIMBIA AND COMPANY

Pulvules Extralin* 0.5 Gm. Twelve pulvules supply the equivalent of 1 U S P oral unit of liver.

U S patent 1,894,247 (Jan 10 1933 expires 1950) U S trade mark 290,233

POWDERED STOMACH—Dried Stomach—The dried and powdered defatted wall of the stomach of the hog *Sus scrofa* Linné var. *Domesticus* Gray (Fam. Suidæ). It contains factors which cause an increase in the number of red blood corpuscles in the blood of persons suffering from pernicious anemia. The approximate anti-anemic potency of Powdered Stomach in pernicious anemia is expressed in U S P Units and conforms to all other provisions outlined under Anti-anemia Preparations.—U S P

For descriptions and standards see U S Pharmacopœia under Powdered Stomach.

Actions and Uses—Dried stomach is used in the treatment of pernicious anemia. See preceding article Liver and Stomach Preparations.

Dosage—The average daily dose should not be less than the amount required to furnish 1 U S P oral unit. Larger doses may be necessary in relapse and in severe or complicated cases. The required doses may be administered in a half glassful of water, milk or fruit juice.

PARKE, DAVIS & COMPANY

Ventriculin 100 Gm and 500 Gm bottles Dried stomach
40 grams of material prepared by the method employed in pro-
ducing the contents of this bottle constitutes 1 U S P unit
(oral)

U S patent 1 937,133 U S trademark 270 811

Solutions for Oral Administration

SOLUTION OF LIVER—Liquid Extract of Liver—
'Contains that soluble thermostable fraction of mammalian
livers which increases the number of red blood corpuscles in
the blood of persons suffering from pernicious anemia The
approximate anti anemic potency of Solution of Liver in per-
nicious anemia is expressed in U S P Units and conforms
to all other provisions outlined under Anti anemia Prepara-
tions' U S P

For description and standards see U S Pharmacopeia under
Solution of Liver

Actions and Uses—Solution of liver is used in the treatment
of pernicious anemia See preceding article Liver and Stomach
Preparations

Dosage—Solution of liver is administered orally The aver-
age daily dose should not be less than the quantity required to
supply 1 U S P oral unit Patients in relapse or with com-
plications often need larger doses which may be more con-
veniently furnished by supplementing or substituting the oral
treatment with the administration of injectable preparations
until the blood picture is restored to normal Like the dry
preparations for oral use solution of liver is better suited for
maintenance therapy and when there is some objection to
repeated injections The solution may be administered with
milk or fruit juice

Solutions for Parenteral Administration

∴ ∴ ∴

or Parenteral Use
in of that soluble
which increases the
of persons suffer

ing from pernicious anemia The approximate anti anemic
potency of Liver Injection upon parenteral administration in
pernicious anemia is expressed in U S P Units and conforms
to all other provisions given under Anti anemia Preparations'
U S P

For description and standards see U S Pharmacopeia under
Liver Injection

Actions and Uses—Liver Injection is used for intramuscular
injection in the treatment of pernicious anemia See preceding
article Liver and Stomach Preparations

Dosage—For the average case in relapse it is usually advisable to administer an initial injection of the amount which will provide 20 to 40 U S P injectable units. This may be divided into daily injections of 10 to 20 units each for two or four successive days depending on the severity of the individual case. In seven to ten days after the initial treatment weekly injections of the amount necessary to furnish 10 U S P injectable units are generally sufficient to induce complete remission. The maintenance dose should not be less than the quantity required to provide 1 U S P injectable unit daily or an equivalent cumulative amount. In complicated cases and those with extensive neurologic involvement the optimum dose may be larger and must be determined for each patient. In patients who are to receive larger doses it may be advisable to divide the required amount and inject one half into each gluteal region.

CHAPTER XVIII

HORMONES AND SYNTHETIC SUBSTITUTES

Adrenal Cortex

The cortex of the adrenal gland is essential for life. Adrenal ectomized animals die in a few days. During the acute stages of adrenal insufficiency occurring in disease or as the result of experimental procedures in animals conditions commonly observed include blood concentration low blood pressure gastro-intestinal disturbances, asthenia subnormal temperature and low basal metabolic rate. There also may be found loss of sodium and retention of potassium in most species loss of carbohydrate

Extracts of the adrenal cortex contain several potent substances which influence to a variable degree electrolyte water or carbohydrate metabolism, however no one of these substances and no synthetic substance has yet been shown to possess all of the effects of a potent cortical extract.

Crystalline compounds have been isolated from the cortex which are capable of maintaining the life of adrenalectomized animals and restoring toward normal the metabolic conditions induced by adrenal insufficiency. These compounds are steroids and the most potent of them are corticosterone and dehydrocorticosterone. Many other steroids have been isolated from this tissue but most of these have little known physiologic activity.

The chemical structure of the cortical steroids is closely related to that of the sex hormones, a fact some of the cortical

similar to those produced by cortical steroids

Adrenal cortex extracts have been assayed in many ways. There are advantages to each of the various methods but it appears that the maintenance of life in the adrenalectomized animal is the most significant measure of activity for such extracts. For purposes of N N R description the Council has recognized the assay method devised by Pfaffner, Swingle and Vars (*J Biol Chem* 104 701, 1934) or the slight modification used by Cartland and Kuzenga (*Am J Physiol* 117 678,

1936) By these methods the activity of adrenal cortex preparations is expressed in terms of dog units for uniformity of labeled potency. An alternate assay method using adrenal ectomized rats according to the procedure of Cartland and Kuizenga (*Am J Physiol* 117 678 1936) may also be employed and the results transposed in terms of dog units, provided sufficient data are presented that such a comparison of assays is justified. No preparation of adrenal cortex extract will be accepted for inclusion in New and Nonofficial Remedies that does not have a minimum of 50 dog units or 25 rat units per 10 cc of extract when assayed by the Cartland and Kuizenga method.

Desoxycorticosterone, one of the components of adrenal cortex but which is prepared synthetically, is capable of maintaining life in adrenalectomized animals. Desoxycorticosterone differs from extracts of the adrenal cortex in being relatively inactive by mouth and in being chiefly concerned with salt and water metabolism. The adrenal cortex has other activities such as a role in the regulation of carbohydrate, fat and protein metabolism. Therapies promising but, as yet, only on a small scale. Indications of this therapy including the contraindications and contraindications is discussed in M. A. 114 2549 (1940).

ADRENAL CORTEX EXTRACT—An extract of adrenal glands, from domesticated animals used as food in man, containing the cortical steroids essential for the maintenance of life in adrenalectomized animals. Only traces of epinephrine are present.

Actions and Uses—Although the extract is active by mouth this method of administration for therapeutic purposes is not to be depended upon in cases of crises. The usual methods of administration are subcutaneous, intramuscular or intravenous injection. The extract is of value in the treatment of Addison's disease or of adrenal insufficiency of other types and in surgical procedures involving the adrenal cortex when prophylactic measures are needed to prevent the development of temporary adrenal insufficiency. There is as yet no conclusive proof of the value of the extract in the so-called borderline cases of adrenal insufficiency.

Dosage—The amount required for therapeutic purposes varies widely according to the condition of the patient, the indications, and during a crisis should govern the dosage. Within a few hours may be substituted in many cases of sodium chloride or other sodium salts etc. in supplementing adrenal cortex extracts.

Preparation —

Adrenal cortex extract is prepared by the method of Cartland and Kuizenga (*J Biol Chem* 116:57, 1936). Frozen adrenal glands are extracted with chilled acetone and the gland residue removed by filtration. The acetone extract is concentrated in vacuo below 45 C and the aqueous fraction so obtained is freed of inactive lipid sub-

Berkfeld filtration

Adrenal cortex extract is assayed biologically according to the Cartland and Kuizenga method (*Am J Physiol* 117:678, 1936). Each cubic centimeter contains not less than 50 dog units (25 rat units) when assayed according to the method of Cartland and Kuizenga. This assay method depends on the maintenance of life in adrenalectomized dogs. The epinephrine content of the extract as determined by the U S P dog blood pressure method is less than 1/200,000.

THE UPJOHN COMPANY

Sterile Solution Adrenal Cortex Extract: 10 cc vials. Each 1 cc contains not more than 3 mg of gland extractives, having a potency equivalent to 50 dog units when assayed by the Cartland-Kuizenga method, in physiological solution of sodium chloride. Preserved with 10 per cent of alcohol.

U S patent 2,053,549 (Sept 8, 1936, expires 1953) and 2,096,342 (Oct 19, 1937, expires 1954).

Adrenal Medulla

(See Epinephrine in Chapter VIII, Autonomic Drugs.)

Ovaries

Sex hormones, as a rule, are closely related chemically. These compounds are also similar in structure to the steroids of the adrenal cortex and other tissues of the body. They possess, likewise, physiological properties common to each other. For instance, certain androgens possess estrogenic or progestational qualities while progesterone is said to have a slight androgenic activity. The steroids of the adrenal cortex may also produce changes in the sex organs of either sex. These probably account for the *virilism*, *feminism* or precocious puberty seen in patients with adrenal cortical tumors.

The ovaries produce internal secretions which are necessary for the proper functioning of the uterus, in particular, for the production of cyclic growth processes of this organ and for the development of the decidua; in addition these internal secretions determine cyclic changes in the vagina and cervix and influence the growth of the mammary gland. There is good

reason for assuming that in addition to intrinsic factors situated in the ovary itself, hormones given off by the anterior pituitary regulate the growth of the follicles, ovulation, and corpus luteum formation

The follicle stimulating hormone of the anterior pituitary induces growth of the graafian follicles. During this period estrogenic hormone is secreted by the follicles (probably from the cells of the theca interna), which evokes certain changes in the accessory organs. The vaginal mucosa thickens and the cells undergo a more intense cornification, the myometrium hypertrophies, while the endometrium changes rather rapidly to the proliferative phase. At this time the duct system of the breast develops to a varying extent. After ovulation there is a release of the luteinizing hormone of the pituitary, and the collapsed follicle becomes transformed into a corpus luteum which secretes progesterin (progesterone). In the human the corpus luteum elaborates estrogenic hormone as well. The progestational hormone induces secretory changes in the endometrium preparatory to nidation, and stimulates growth of the alveolar breast tissue. Menstruation is often claimed to result from the sudden failure of corpus luteum activity, the collapse of the endometrial structure producing the subsequent extravasation of menstrual blood. There are several discrepancies to this theory, and menstruation has not as yet been completely explained.

Estrogen The injection of potent estrogenic substances in castrate animals will induce changes in the accessory sex organs which are typical of estrus. Long continued injections, however, induce hypertrophic then metaplastic changes in the uterus, cervix and breast. It is often considered that clinical endometrial hyperplasia, chronic cystic mastitis and fibromyomas are due to long continued estrogen secretion by the ovary.

Estrogenic substance is also responsible for the contractility of the uterus and the sensitivity of the myometrium to oxytocic agents. It has recently been shown that the smooth muscle of the human Fallopian tube is also responsive to estrogenic substance.

The excretion curve of estrogenic substances in the normally menstruating women is irregular and varies extremely from day to day. In general, however, there are two peaks, one at the height of follicular activity and one before menstruation. Excretion curves in ovarian disorders have not been adequately studied at the present time because of numerous technical difficulties in assays. During pregnancy large amounts of estrogens are excreted in the urine in the form of water soluble conjugate. In pregnant women these are in the form of glucuronides and in pregnant mares in the form of sulfates. Hydrolysis of the urine, either by acid or by putrefaction, converts the conjugated estrogens into their free forms which are more active physiologically.

Estrogenic substances occur widely in nature, in plants as well as in animals. Estrone (ketohydroxyestrin) and estrinol (trihydroxyestrin) are extracted from pregnancy urine or placentas of humans while several estrogens including estrone, equilin and hippulin, are obtained from the urine of pregnant mares. Sow's ovaries contain both estrone and estradiol (dihydroxyestrin), but not in sufficient quantities to make them a worthwhile source commercially. Estradiol exists in two stereoisometric forms—alpha and beta. The alpha estradiol is probably the most potent of all known estrogens, the beta form is

palmitate) have therefore been prepared to meet this purpose.

Estrogens may be administered with a suitable base of considerable activity. Administered in the form of an amount of its preparation have been prepared which administered orally. This is a completely synthetic product which has proved effective therapeutically by the oral route. (For further information see J. A. M. A. 107:1175 [Oct. 4] 1941).

Besides crystalline estrogens, preparations of highly purified but noncrystalline estrogens are available. These are usually extracted from the urine of pregnant women or pregnant mares; the estrogenic activity of such extracts is due almost entirely to estrone. The Council has coined the term Solution of Estrogens for such preparations.

There has been an enormous amount of clinical research with estrogenic substances. Claims for therapeutic results have been often exaggerated and confusing. Definite and consistently reliable results have been obtained in only a relatively small number of conditions. All other indications should be considered unscientific or in the experimental stage of therapy.

Estrogens are carcinogenic when administered experimentally to animals which have an inherited sensitivity to the development of mammary carcinoma. Many clinicians believe that estrogens are therefore contraindicated in the treatment of women who have a familial or personal history of mammary or genital malignancy.

Progesterone. The hormone of the corpus luteum—induces secretory changes of the endometrium, stimulates growth of the mammary alveolar tissue and relaxes the uterine smooth muscle. It is essential for nidation of the ovum and the maintenance of pregnancy. During gestation the ovary elaborates progesterone only through the third month after which the placenta is responsible for its elaboration. Progesterone is not excreted as such but in the form of pregnandiol glycuconide, and is found in the urine of pregnancy or during the corpus

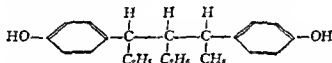
luteum phase of the normal cycle. Studies on habitual abortion have revealed that pregnandiol excreted in the urine may be abnormally low at about the hundredth day of gestation indicating an insufficiency of progesterone. It has been calculated that the administration of 10 mg of progesterone daily is required to bring the pregnandiol level to normal.

A substance which has progestational activity when administered orally has recently appeared on the market. It is crystalline anhydro hydroxy progesterone. There is increasing evidence in the literature to indicate its therapeutic value at the present time.

Commercial preparations of progesterone are either extracts of animal ovaries or the pure compound prepared synthetically. At one time there was considerable enthusiasm over the therapeutic use of such preparations in dysmenorrhea, menorrhagia and habitual abortion, but the volume of satisfactory evidence is too small to warrant dependence on progesterone for treatment of these conditions. The Council has not accepted progesterone or any preparation of this principle.

Crystalline Estrogens

BENZESTROL—Octofollin—24 di (*p* hydroxyphenyl) 3 ethyl hexane— $C_{20}H_{28}O_2$ —M W 298.41. Benzestrol is one pair of racemates of the synthetic substance possessing the following structural formula:



Actions and Uses—This compound when introduced into the human body orally and by injection provokes a response similar to that caused by other estrogenic substances. It is claimed to have a low incidence of toxicity. Contraindications are similar to those of other estrogens.

Dosage—By biologic assay 1 mg of benzestrol is reported to be equivalent to approximately 25 000 international units or to 1 250 rat units of estrone. Average dose in tablets is about 2 or 3 mg and in injection from 2 to 5 mg. This may be repeated daily for four to seven days until the dosage requirement is determined by clinical observation.

Tests and Standards—

Benzestrol is an odorless white crystalline powder which melts at from 162 to 166 C. It is readily soluble in acetone, ether, ethanol, methanol and dilute sodium hydroxide solution, soluble in vegetable oils, moderately soluble in glacial acetic acid, slightly soluble in benzene, chloroform, petroleum ether and dilute ethanol, practically insoluble in water and in dilute mineral acids.

Dissolve 10 mg of benzestrol in 2 cc of concentrated sulfuric acid; a pale yellow color is produced which persists on dilution with water.

(distinction from diethylstilbestrol, which yields an orange color) Add a few drops of 50 per cent solution of antimony pentachloride in dry alcohol free chloroform to a very dilute solution of benzeestrol in the same solvent a green colored solution which rapidly changes to brown is produced (distinction from diethylstilbestrol, which yields a red or bluish red color).

1
4
1
1
2
1

Dissolve 0.1 Gm of benzeestrol in 5 cc of ether the solution is clear and colorless Dissolve 0.1 Gm of benzeestrol in 5 cc of previously

" " " " " "

Transfer 0.1 Gm of benzeestrol accurately weighed to a 100 cc

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normal bromide bromate solution down the wall of the flask and quickly insert the stopper, avoiding possible loss of bromine vapor Shake the flask and contents thoroughly for several minutes Place about 5 cc of 10 per cent potassium iodide solution around the stopper and let the flask stand in the dark for thirty to forty minutes at 25 to 30 C At the end of this period allow the sodium iodide solution to enter the flask, avoiding loss of vapor from within; place 3 to 5 cc of distilled water around the stopper and allow it to rinse in the sodium iodide solution Stopper the flask tightly and shake thoroughly Let the mixture stand for five minutes and then titrate with tenth normal sodium thiosulfate solution shaking the mixture thoroughly after each addition of the reagent The end point of the titration is reached when on addition of a fraction of a drop of the sodium thiosulfate solution followed by thorough shaking of the mixture the pink color of iodine in the carbon tetrachloride layer disappears Each cubic centimeter of tenth normal bromide bromate solution is equivalent to 3.730 mg of benzeestrol the amount of benzeestrol found is not less than 99 per cent nor more than 101 per cent

LEDERER LABORATORIES

Solution Benzeestrol (in Sesame Oil) 5 mg per cc.:
2 cc vials Preserved with 0.5 per cent chlorobutanol

Tablets Benzeestrol: 2 mg and 5 mg

SCHIEFFELIN & Co.

Solution Benzeestrol: 10 cc multiple dose, rubber capped vials, 5 mg per cc.

Tablets Benzeestrol: 0.5 mg, 10 mg, 20 mg and 50 mg

Vaginal Tablets Benzeestrol: 0.5 mg

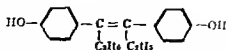
DIETHYLS

4'-stilbenediol —

(M W. 268.34)

not less than 98

estrol has the following structural formula



For description and standards see the First Bound Supplement U S Pharmacopeia XII under Diethylstilbestrol, Diethylstilbestrol Capsules, Diethylstilbestrol Injection and Diethylstilbestrol Tablets

Actions and Uses—Dodds and his co workers, after extensive experimentation with synthetic substances, recognized the estrogenic activity of the stilbene compounds. Diethylstilbestrol is the most potent of these compounds described up to the present time. It may be prepared in a variety of ways from nonbiologic, organic chemicals. Its physiologic activity duplicates practically all the known actions of natural estrogens. Thus it induces estrus in rodents, stimulates the growth of the endometrium and myometrium, primes the endometrium for progestational changes, causes reddening of the "sex skin" of monkeys and feminization of the plumage of birds, induces growth of mammary ducts in female and male animals as well as in human beings, raises the blood fat and calcium in fowl, induces uterine bleeding in castrate animals and human beings and suppresses ovulation as well as inhibits the secretion of various factors of the anterior pituitary gland, resulting in stunting of growth, inhibition of lactation and atrophy of the gonads. It differs in its action from natural estrogens in its inability to cause the ovipositor reaction of the female bitterling and to antagonize the action of androgens on comb growth of capons. The therapeutic use has been demonstrated to be effective for all those conditions recognized to respond to the natural estrogens. Various modifications of diethylstilbestrol have been devised, such as fatty acid esters and a number of ethers, for increasing the estrogenic efficiency of this substance. These are at present the subject of clinical and physiologic investigations. Diethylstilbestrol possesses the advantage of being relatively active by mouth as well as percutaneously. The ratio of potency between oral and parenteral administration varies in the hands of different investigators from 1/2 to 1/5 in the human being as well as in rodents. In the therapeutic use of diethylstilbestrol there may be a significant incidence of side reactions, the most common of these being nausea, vomiting and headache. It has been considered that these were the result of tissue damage, but no evidence has been presented that therapeutic amounts are actually harmful to human beings and there appears to be conclusive evidence that

experimentally diethylstilbestrol is not significantly more toxic than the natural estrogens. It is now considered that the unpleasant symptoms arising from diethylstilbestrol administration are systemic in origin rather than local probably because of its rapid absorption into the blood stream since few untoward symptoms are observed with the use of diethylstilbestrol compounds which are slowly absorbed from the site of administration.

Diethylstilbestrol is used for the same conditions for which estrogenic substances are employed.

Dosage—The average therapeutic dose for the treatment of menopausal symptoms is 0.5 to 1.0 mg daily by mouth, although it is advised to start with smaller doses for patients who tend to develop disagreeable symptoms. Courses of therapy with periods of a few weeks of no treatment are recommended by some authorities. Injection of similar quantities of diethylstilbestrol may be used weekly or daily. For vaginal use, 1 vaginal tablet of a similar strength may be used.

to those for natural estrogens namely familial or personal history of malignancy of the reproductive organs.

ABBOTT LABORATORIES

Diethylstilbestrol (in peanut oil) 0.5 mg per cc and 1.0 mg per cc respectively 1 cc ampul

Tablets Diethylstilbestrol 0.1 mg 0.25 mg 0.5 mg 1 mg and 5 mg

Vaginal Suppositories Diethylstilbestrol 0.1 mg and 0.5 mg

GEORGE A. BRON & COMPANY, INC.

Diethylstilbestrol (in vegetable oil) 1.0 mg per cc 1 cc ampul

Caplets Diethylstilbestrol 0.2 mg 0.5 mg 1 mg and 5.0 mg

Suppositories Diethylstilbestrol 0.5 mg

Tablets Diethylstilbestrol 5.0 mg

THE DRUG PRODUCTS CO., INC.

Pulvules Diethylstilbestrol 0.1 mg and 1 mg

Hyposols Diethylstilbestrol (in oil) 0.5 mg, 1 mg and 5 mg 1 cc in sesame oil

Hyposols Diethylstilbestrol (in oil) 0.5 mg and 1 mg per cc 30 cc and 5 mg per cc 10 cc in sesame oil with 0.5 per cent chloroform and anhydrous

ENDO PRODUCTS, INC

Diethylstilbestrol (in sesame oil) 0.5 mg per cc 10 mg per cc 20 mg per cc and 50 mg per cc 1 cc ampuls

LAKESIDE LABORATORIES INC

Diethylstilbestrol (in sesame oil) 0.5 mg per cc 10 mg per cc 50 mg per cc 1 cc ampuls each containing 0.5 per cent chlorobutanol

Tablets Diethylstilbestrol 0.25 mg 0.1 mg 0.5 mg 10 mg and 50 mg

LIEDERLE LABORATORIES INC

Diethylstilbestrol (in sesame oil) 1 mg per cc 0.5 cc and 1 cc ampuls

Capsules Diethylstilbestrol 0.1 mg 0.5 mg and 10 mg

ELI LILLY AND COMPANY

Diethylstilbestrol (in cottonseed oil) 0.25 mg per cc 0.5 mg per cc 1 mg per cc and 5 mg per cc 1 cc ampuls

Suppositories Diethylstilbestrol 0.1 and 0.5 mg

Tablets Diethylstilbestrol 0.1 mg 0.25 mg 0.5 mg 1 mg and 5 mg

THE WM S MERRELL COMPANY

Diethylstilbestrol (in corn oil) 1 mg per cc 20 cc vial containing 0.5 per cent chlorobutanol

Tablets Diethylstilbestrol 10 mg and 0.2 mg

SMITH DORSEY COMPANY

Diethylstilbestrol (in peanut oil) 0.5 mg per cc and 1 mg per cc 1 cc ampuls

Tablets Diethylstilbestrol 0.1 mg 0.5 mg and 1 mg

E R SQUIBB & SONS

Tablets Diethylstilbestrol 0.25 mg 0.1 mg 0.5 mg 10 mg and 50 mg

FREDERICK STEARNS & COMPANY DIVISION

Tablets Diethylstilbestrol 0.1 mg 0.5 mg and 10 mg

THE UPJOHN COMPANY

Sterile Solution Diethylstilbestrol (in vegetable oil) 0.5 mg per cc and 10 mg per cc 1 cc ampuls

Perles Diethylstilbestrol 01 mg 0.25 mg 05 mg
10 mg and 50 mg

Suppositories Diethylstilbestrol (Juvenile Size) 01 mg
and 05 mg (ad lt size)

WALLACE & TIERNAN PRODUCTS INC

Tablets Diethylstilbestrol 01 mg 05 mg and 10 mg

WILLIAM R WARNER & Co INC

Tablets Diethylstilbestrol 01 mg and 1 mg

Diethylstilbestrol (in oil) 1 mg per cc 1 cc ampuls

Diethylstilbestrol (in oil) 1 mg per cc 10 cc. multiple
dose serum capped vials containing 05 per cent chlorobutanol

WARREN TRFED PRODUCTS COMPANY

Sterilized Solution Diethylstilbestrol (in sesame oil)
1 mg per cc 1 cc. ampuls and 15 cc bottles containing 05 per
cent chlorobutanol

Tablets Diethylstilbestrol 05 mg and 1 mg

WINTHROP CHEMICAL COMPANY INC

Diethylstilbestrol (in sesame oil) 05 mg per cc and
1 mg per cc 1 cc ampuls

Suppositories Diethylstilbestrol 01 mg and 05 mg

Tablets Diethylstilbestrol 01 mg 05 mg 1 mg and
5 mg

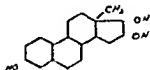
WORTH INCORPORATED

Diethylstilbestrol (in corn oil) 10 mg per cc 1 cc
ampuls

Suppositories Diethylstilbestrol 01 mg and 05 mg

Tablets Diethylstilbestrol 01 mg 05 mg and 025 mg

nonproprietary synonyms



Actions and Uses—Estriol (theelol) is used orally for the same conditions for which estrogenic substances are employed

Dosage—Orally from 0.06 to 0.12 mg from one to four times a day, alone or as supplement to parenteral therapy

Tests and Standards—

Estriol occurs as a white odorless, microcrystalline powder. During heating on the microscopic heating stage, rearrangement of the crystal structure takes place at 270 C and 275 C. The substance melts sharply at 282 C (rate of heating, U S P XI, 4 degrees in one minute—Kofler microscopic heating stage). Twenty mg of estriol heated for five hours at 80 C under vacuum of 2 mm over phosphorus pentoxide is practically insoluble in oils. Transfer weighed to a 1 cc of distilled dioxane and determine the optical rotation after the U S P XI method page 459, using a 2 dm microtube. The specific rotation $[\alpha]_D^{25}$ is + 58 degrees (\pm 5 degrees).

Dissolve approximately 0.06 Gm of estriol, accurately weighed, in a pyridine (6 cc) and acetic anhydride (2 cc) mixture (3:1) and heat under a micro reflux condenser for twenty-four hours at 95 C. Transfer the solution to a 250 cc flask containing 100 cc of ice-cold water and titrate with 0.1 normal sodium hydroxide; the acetic acid value is not more than 129 nor less than 121, equivalent to three acetylated hydroxyl groups. [A blank determination must be made for pyridine, acetic acid and anhydride] (J Biol Chem 61:655, 1931).

Dissolve approximately 0.04 Gm of estriol in a pyridine (6 cc) and acetic anhydride (2 cc) mixture (3:1) and heat under a micro reflux condenser for twenty-one hours at 95 C. Let stand at 37 C for another twenty-four hours. Add 10 cc of 50 per cent alcohol and evaporate under vacuum to a thick syrup. Add very gradually about 1 cc of alcohol and set aside for crystallization. Filter the crystals and redissolve in 3 cc of 95 per cent alcohol. Evaporate the alcohol and dissolve the residue in 4 cc of pyridine. After addition of 16 cc of water a white flocculent precipitate occurs; recrystallize twice from 90 per cent alcohol, dry the crystals in vacuum at 80 C over phosphorus pentoxide; the melting point of the triacetate is 126 C (\pm 1 degree).

... weighed, to a ...
... sulfuric acid
... in Micro
... gives a
... than 74.6
per cent, and a hydrogen content of not more than 8.7 per cent, nor less than 8.0 per cent.

Estriol crystals exhibit a reddish fluorescence under filtered ultra violet light.

The dosage forms of brands of estriol are biologically assayed, the assay being under control of the St. Louis University committee.

Estriol is manufactured under license from St. Louis University under U S patents 1,967,350 and 1,967,351 (July 24, 1934, expire 1951).

ABBOTT LABORATORIES

Capsules Estriol 0.12 mg and 0.24 mg

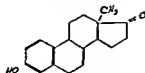
ELI LILLY AND COMPANY

Pulvules Estriol: 0.06 mg, 0.12 mg and 0.24 mg

PARKE, DAVIS & COMPANY

Kapseals Theelol 0.12 mg and 0.24 mg

ESTRONE—Theelin— $C_{18}H_{26}O_2$ —U S P



For description and standards see the U S Pharmacopeia under Estrone

Actions and Uses—Estrone is used for the same conditions for which estrogenic substances are employed

Dosage—In disturbances of the menopause 0.2 mg (2000 I U) to 10 mg (10000 I U) injected intramuscularly one or more times weekly depending on the response of the patient. After producing relief dosage may be lowered to a maintenance level. As much as 50 mg (50000 I U) per week may be required in resistant cases of kraurosis vulvae. Estrone suppositories are valuable adjuncts in the treatment of senile vaginitis.

Occasionally a considerable amount of uterine bleeding occurs in menopausal women following large doses of estrone. This may be quite alarming at times and it is, therefore, advisable to reduce the dose of estrone as soon as feasible.

For gonorrheal vaginitis in children from 0.02 to 0.2 mg (200 to 2000 international units) in glycerogelatin suppositories daily or as required. This may be supplemented by intramuscular injection of small doses of the oil solution if necessary. Changes in the secondary sex organs may be produced by this therapy particularly if it is too prolonged. These changes usually regress on cessation of treatment.

Estrone is effective by mouth if the dosage is adequate.

Estrone is manufactured under license from St. Louis University under U S patents 1967350 and 1977351 (July 24 1934 expire 1951).

ABBOTT LABORATORIES

Estrone (in oil) an amp 0.2 mg in 1 cc (2000 international units) 0.5 mg in 1 cc (5000 international units) and 1 mg in 1 cc (10000 international units). Ampuls 2 mg each cubic centimeter contains 0.2 mg with 1 cc.

Vaginal Suppositories Estrone 0.2 mg is a glycerogelatin base.

ELI LILLY AND COMPANY

Estrone (in cotton seed oil) Ampuls 0.1 mg in 1 cc (1 000 international units) 0.2 mg in 1 cc (2 000 international units), 0.5 mg in 1 cc (5 000 international units) and 1 mg in 1 cc (10 000 international units)

Vaginal Suppositories Estrone 0.2 mg (2 000 international units) in a glycerin base

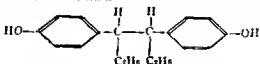
PARKE, DAVIS & COMPANY

Theelin (in peanut oil) Ampuls 0.1 mg in 1 cc (1 000 international units), 0.2 mg in 1 cc (2 000 international units) 0.5 mg in 1 cc (5 000 international units) and 1 mg in 1 cc (10 000 international units)

Theelin Aqueous Suspension 2 mg in 1 cc ampuls (20 000 international units)

Vaginal Suppositories Theelin 0.2 mg (2 000 international units) in glycerogelatin base

HEXESTROL—Meso 3,4-di-*para*hydroxyphenyl *n*-hexane $C_{20}H_{22}O_2$ (M W 270.36) Hexestrol may be represented by the following structural formula



It may be prepared from anethole in ether solution by (a) treating with anhydrous hydrogen bromide to form anethole hydrobromide (b) conversion of the anethole hydrobromide to 3,4-dianisylhexane by means of metallic magnesium, aluminum, copper or zinc turnings and (c) hydrolysis of the 3,4-dianisylhexane to form hexestrol. The product thus obtained may be purified by recrystallization from dilute alcohol.

Actions and Uses—Hexestrol is used for the same conditions for which estrogenic substances are employed. It is claimed to cause a lower incidence of toxic symptoms than those which follow diethylstilbestrol administration.

Dosage—As is the case with all estrogenic substances the dosage of hexestrol must be adjusted to the individual case. As a guide the following dosages may be satisfactory. For menopausal symptoms 20 to 30 mg daily by mouth until symptoms are under control and then 0.2 to 10 mg daily as a maintenance dose or by injection 10 mg in oil three times weekly with similar lowering for maintenance of control. For gonorr

times weekly by injection suppression of lactation 150 mg one to three times daily for two or more days or 150 mg in oil daily for two or more days by injection

Tests and Standards—

Hexestrol occurs as an odorless white crystalline powder which melts at 185-188 C. It is freely soluble in ether, soluble in acetone, ethanol and methanol, slightly soluble in benzene and chloroform, practically insoluble in water and in dilute mineral acids. It may be dissolved in vegetable oils and in dilute solutions of sodium or potassium hydroxide. When recrystallized from diluted alcohol hexestrol appears in the form of thin platelike crystals of irregular serrated outline.

Dissolve about 10 mg of hexestrol in 10 cc of dilute alcohol and add three drops of 1 per cent ferric chloride solution; a yellowish green color develops which changes to yellow. Add a few drops of 50 per cent solution of antimony pentachloride in dry alcohol free chloroform to a very dilute solution of hexestrol in the same solvent; a red colored solution is produced. Dissolve 10 mg of hexestrol in 5 cc of concentrated sulfuric acid; no color is produced (distinct on from diethylstilbestrol which yields an orange color).

The hexestrol diacetate obtained in the assay given below melts at 137-139 C.

Dry an accurately weighed specimen of hexestrol to constant weight.

Transfer to a suitable flask about 0.5 Gm. of dried hexestrol accurately weighed, and add 2 cc. of acetic anhydride, and 4 cc. of dry

Transfer to a suitable flask about 0.5 Gm. of dried hexestrol accurately weighed, and add 2 cc. of acetic anhydride, and 4 cc. of dry

Transfer to a suitable flask about 0.5 Gm. of dried hexestrol accurately weighed, and add 2 cc. of acetic anhydride, and 4 cc. of dry

THE W. S. MERRILL COMPANY

Tablets Hexestrol 0.2 mg., 10 mg. and 30 mg.

THE W. S. MERRILL CO., LOEWEN LABORATORY DIVISION

Solution Hexestrol in Oil 1 mg. per cc. 20 cc. ampuls
Prepared with 0.5 per cent chlorobutanol

Solution Hexestrol in Oil 5 mg. per cc. 20 cc. vials
Preserved with 0.5 per cent chlorobutanol

Non Crystalline Estrogens

ESTROGENIC SUBSTANCES (Water insoluble)—

Amniotin—A highly concentrated, noncrystalline preparation of estrogen (ketohysterone) together with a small varying amount of other estrogenic principles ketone extracted from the urine of pregnant mare.

Actions and Uses—Estrogenic substances are used either orally, intravaginally or by hypodermic injection of an oil solution in a considerable variety of conditions associated with deficiency of estrogens. These include treatment of the symptoms of the menopause syndrome, natural or artificial, senile vaginitis, kraurosis vulvae, pruritus vulvae, and gonorrheal vaginitis of children. A related use is in the treatment of hypogenitalism in the female, but consideration should first be given to the possibilities of relieving such a condition by other means, such as gonadotropic therapy, which would cause the ovaries to function more normally. The use of estrogen in such conditions must be understood as substitution for ovarian function, not as stimulating such activity. Estrogens have been used in attempts to inhibit production of gonadotropic hormone by the anterior pituitary. This result requires very large doses. For a time it was thought that large doses of estrogen inhibited lactation immediately post partum. This is doubted but estrogenic therapy has been found helpful in relieving the engorgement of breasts especially when lactation is to be suppressed.

It has been found possible to interrupt the prolonged or excessive flowing of many women with functional bleeding by brief courses of intensive estrogenic therapy. This is considered safe practice only when the interval of freedom from bleeding is used to eliminate local pelvic lesions as the cause of the flowing. The subsequent administration of sequences of estrogenic substances and progesterone* to reestablish cycles of flowing is a possible method of alleviating a condition which is widely believed to result from deficiency of one or both of the ovarian hormones.

Estrogenic materials have been reported to act together with or as a substitute for castration in the palliation of the local discomforts from prostatic carcinoma and its metastases. The action is apparently not curative but may persist for a number of months.

Dosage—From 2 000 to 20 000 international units injected one or more times weekly depending on the response of the patient. After relief has been produced, dosage may be lowered to a maintenance level. As much as 15,000 international units per week may be required in resistant cases of kraurosis vulvae. Suppositories of estrogenic substances are valuable adjuncts in the treatment of senile vaginitis.

* If uterine bleeding occurs
 ses of any estrogenic
 times and it is there
 soon as feasible

For gonorrheal vaginitis in children from 1 000 to 2 000 international units daily in glycerogelatin suppositories may be required. This may be supplemented by intramuscular injection of small doses of the oil solution if necessary. Change

in the secondary sex organs may be produced by this therapy, particularly if it is too prolonged. These changes usually regress on cessation of treatment. Estrogenic products must be used with care.

Capsules or tablets of estrogenic substances, 1,000, 2,000, 4,000 or 10,000 international units, one or more times daily, may be administered orally alone or as a supplement to parenteral therapy.

Preparation —

Urine from pregnant mares collected after the fifth month of pregnancy, is acidified with hydrochloric acid to pH 3 and boiled for three hours. The hydrolyzed urine is extracted with ethylene dichloride, and the extract evaporated to dryness. The residue is dissolved in ether, the ether solution is washed with half saturated sodium carbonate solution, followed by tenth normal sodium hydroxide and finally the ether removed by distillation. This residue is dissolved in toluene and the active material is extracted from the toluene with normal sodium hydroxide. This alkaline extract after neutralization with hydrochloric acid is extracted with toluene and the toluene solution after washing with water is evaporated to dryness.

This residue is further purified by high vacuum fractional distillation. The resulting residue is dissolved in sterile vegetable oil for hypodermic and oral use and incorporated in a glycerogelatin base for vaginal administration.

Estrogenic substances are assayed by a modification of the Coward and Burn method in direct comparison with the international standard. The potency is expressed in terms of the international unit. One international unit is defined by the League of Nations Health Organization as the specific estrus producing activity contained in 0.1 microgram (0.0001 mg.) of the standard crystalline ketohydroxy ratin (Culin[®] 34). The physiologic criterion of activity is the appearance of cornified cells in the vaginal smear of a castrated rat.

GRAND A. BREON & COMPANY, INC.

Solution Estrogenic Substances (in Oil) 1 cc. ampula available as 2,000 international units per cc., 5,000 international units per cc., 10,000 international units per cc. of estrogenic substance, 10 cc. rubber stoppered vials containing per cc. 2,000 international units of estrogenic substance and 10 cc. vial (with chlorobutanol 3 per cent), containing per cc. 10,000 international units of estrogenic substance and 30 mg. of chlorobutanol as a preservative.

Solution of Estrogenic Substance (in oil) with Chlorobutanol 3%. 10 cc. vial. Each cubic centimeter contains 2,000 international units of estrogenic substance and chlorobutanol 3 per cent.

BENTON LABORATORIES, INC.

Solution of Estrogenic Substance (in oil) 1 cc. size ampul containing 1 cc. equivalent of 2,000 international units per cubic centimeter, 5,000 international units per cubic centi-

meter, 10,000 international units per cubic centimeter or 20,000 international units per cubic centimeter of estrone in sesame oil with benzyl alcohol 3 per cent

Solution of Estrogenic Substances (in oil) with Benzyl Alcohol 3%: 10 cc. and 30 cc vials, each being available in potencies containing the equivalent of 2,000 international units per cubic centimeter, 5,000 international units per cubic centimeter, 10,000 international units per cubic centimeter, and 20,000 international units per cubic centimeter of estrone in sesame oil with benzyl alcohol 3 per cent

LAKESIDE LABORATORIES, INC

Sterile Solution of Estrogenic Substances (in Sesame Oil): 1 cc ampul containing the equivalent of 2,000 international units per cubic centimeter, 5,000 international units per cubic centimeter, 10,000 international units per cubic centimeter, and 20,000 international units per cubic centimeter of estrone in sesame oil with benzyl alcohol 3 per cent

Tablets Estrogens: 1,000 international units, 2,000 international units and 4,000 international units

SHARP & DOHME, INC.

Sterile Solution of Estrogenic Substances (in oil) 1 cc size ampuls containing the equivalent of 2,000 international units per cubic centimeter, 5,000 international units per cubic centimeter or 10,000 international units of estrone per cubic centimeter in peanut oil

Capsules Estrogenic Substances (in oil): 1,000 international units, 2,000 international units or 4,000 international units of estrone in peanut oil

SMITH-DORSEY COMPANY

Sterile Solution of Estrogenic Substances (in Peanut Oil): 1 cc ampul containing the equivalent of 2,000 international units per cc, 5,000 international units per cc, and 10,000 international units per cc of estrone, 10 cc ampul containing in each cc the equivalent of 20,000 international units of estrone with 3 per cent benzyl alcohol added as a preservative, and 10 cc ampul-vial containing in each cc the equivalent of 10,000 international units of estrone

Solution Estrogenic Substances (in Sesame Oil) with Benzyl Alcohol 3%: 1 cc ampul containing the equivalent of 2,000 international units per cc, 5,000 international units per cc and 10,000 international units per cc of estrone, 10 cc ampuls containing in each cc the equivalent of 20,000 international units of estrone with 3 per cent benzyl alcohol added as a preservative, and 10 cc ampul-vial containing in each cc the equivalent of 10,000 international units of estrone

E. R. SQUIBB & SONS

Amniotin (in Corn Oil) 1000 international units per 5 cc ampuls Available as 5000 international units per 10 cc vials containing international units per cc

Amniotin Pessaries 1000 international units and 2,000 international units respectively, in a glycerogelatin base

Capsules Amniotin 1000 international units 2000 international units 4000 international units and 10 000 international units

Trademark 318 536

WYETH, INCORPORATED

Solution Estrogens (in Corn Oil) 5 cc ampuls Available as 5000 international units 10000 international units and 20000 international units of estrogen Preserved with 0.5 per cent phenol

ESTROGENIC SUBSTANCES (Water soluble)—**Premarin**—An amorphous preparation containing the naturally occurring water soluble, conjugated forms of the mixed estrogens obtained from the urine of pregnant mares

The principal estrogen present in estrogenic substances (water soluble) is sodium estrone sulfate Varying small amounts of other equine estrogens and relatively large quantities of non-estrogenic material are also present in the mixture The total estrogenic potency of the preparation is expressed in terms of an equivalent quantity of sodium estrone sulfate

Actions and Uses—Water soluble estrogenic substances are used in the same conditions for which other estrogenic substances are employed.

Dosage—For the control of menopausal symptoms, 1.25 mg is usually sufficient If after a few days of treatment the response is not satisfactory, the dose may be increased After symptoms have been brought under control the dosage can usually be reduced For the treatment of senile vaginitis kraurosis vulvae and pruritus vulvae 1.25 to 3.75 mg daily should be sufficient

Preparation—

sodium hydroxide, then twice with small volumes of water and then concentrated to a small volume under reduced pressure at 40 to 50 C.

The concentrate is taken up in acetone and, after the insoluble material has been removed, the acetone solution is concentrated to a small volume. The acetone concentrate is treated with an excess of ether and the precipitate obtained is removed and dried. This precipitate, which varies in color from reddish brown to almost white, is an amorphous, hygroscopic powder possessing a characteristic odor. It is soluble in water, dissolving freely to form a pale yellow solution soluble in alcohol and acetone, insoluble in benzene and ether.

Estrogenic substances (water soluble) may also be removed from the urine of pregnant mares by selective adsorption and elution. The eluate may be purified by solvent partition and finally reduced to powder in a vacuum dryer.

Estrogenic substances (water soluble) are assayed chemically by a modification of the phenol sulfonic acid colorimetric method introduced by Hober and biologically by oral administration to adult ovariectomized rats, using the technique of Kohn and Doloy. The standard of reference for the chemical assay is the international standard for estrone. This standard being inapplicable to the biologic assay of conjugated estrogens in the rat assay biologic variation is controlled by the use of a house standard preparation of conjugated estrogens.

AYERST, McKENNA & HARRISON, LTD

Premarin Tablets: 0.63 mg and 1.25 mg

U. S. trademark 397,925

Pancreas

The pancreas is a gland having, in general, two functions (1) It secretes into the intestine a digestive juice containing the enzymes trypsin, lipase and amylase; (2) it secretes into the blood a hormone, insulin, which regulates the process of carbohydrate metabolism.

When insulin secretion is deficient, or possibly when there is an overproduction of sugar due to other causes, diabetes develops. In this disease the percentage of sugar increases in the blood (hyperglycemia) so that sugar overflows into the urine (glycosuria). The hyperglycemia is associated with a breakdown of the first and last stages in the metabolism of sugar, as revealed, respectively, by failure of glycogen to be deposited in the liver and by failure of the respiratory quotient to become increased when carbohydrate food is ingested. The depression in carbohydrate metabolism may be accompanied by

intra
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but

experimental evidence suggests that besides increased oxidation of sugar, increased storage as glycogen in the liver and possibly in the muscles is a factor in the result. When the percentage of blood sugar falls below the kidney threshold in the diabetic patient, sugar disappears from the urine. If an overdose of insulin is given, the blood sugar falls to a subnormal level, and characteristic symptoms are observed. The level at which these

symptoms occur depends not only on the extent but also on the rate of fall. If the blood sugar has been persistently high and is rapidly reduced, hypoglycemic symptoms may appear at a much higher level of blood sugar than when the fall is slower and more gradual. These symptoms are due to the diminished sugar in the blood as shown by the fact that they are relieved by the replacement of the sugar by oral or intravenous administration.

Clinical assays conducted on patients with uncomplicated diabetes on certain standard dietary regimens reveal that one insulin unit will on an average promote the metabolism of approximately 15 Gm of dextrose. The physician may, therefore gauge his insulin dose with some precision. To do so he must know how much dextrose the patient will derive from his food and metabolism and how much insulin the patient himself can provide from his insulin making tissues. The latter may be determined by measuring the patient's ability to utilize carbohydrate without extra insulin. In any case insulin injections must be made at regular intervals and must be supplemented by accurately weighed diets of known composition.

When properly employed insulin is a specific in the treatment of diabetic coma and acidosis. It is of pronounced value in the management of diabetic patients undergoing surgery and of those with complicating infectious diseases. It makes possible freedom from glycosuria and good mental and physical vigor for patients with severe diabetes.

There is as yet no positive evidence that treatment with insulin will arrest the diabetic process by restoring the patient's antidiabetic function. In the severer cases the evidence now available is against such an assumption. In the milder cases in which insulin has been used the evidence is difficult of interpretation because such patients may show very marked improvement in their ability to utilize carbohydrate on dietary regulation and exercise alone.

Oral Administration of Pancreatic Preparations—In diabetes reliance on the oral administration of the pancreatic preparations thus far prepared has no justification and such practice merits the most vigorous condemnation. Many reputed antidiabetic pancreatic preparations are on the market with claims that they are effective if taken by mouth. The most widely heralded of them have been subjected to the scrutiny of clinical tests controlled with simultaneous laboratory investigation. *None of these thus tested has shown any effect on blood sugar or glycosuria.* Completely negative results were obtained when these preparations were given in the doses recommended by their exploiters as well as in doses twenty times as large. The claim that such preparations exert in some mysterious manner a rejuvenating or stimulating action on the diseased pancreas is based on uncontrolled clinical observation.

Insulin Labeling Regulations

Regulations concerning the certification of batches of drugs composed wholly or partly of insulin are presented in the 8 Federal Register 11837, Aug 27, 1943. Of special interest to the physician are statements on labeling. Each package must contain on the outside wrapper information on the batch mark, strength of the drug in terms of U S P units of insulin per cc., expiration date, and the warning 'Keep in a cold place. Avoid freezing'. The circular or other labeling must contain special information for the guidance of the physician. The outside containers or wrappers must be distinguished by various colors.

Insulin U S P is distinguished by

Yellow, if it contains 20 U S P Units of insulin per cubic centimeter

Red, if it contains 40 U S P Units of insulin per cubic centimeter

Green, if it contains 80 U S P Units of insulin per cubic centimeter

Orange, if it contains 100 U S P Units of insulin per cubic centimeter

If the master lot used was in crystalline form the distinguishing colors may be

Blue and gray or blue, gray and yellow, if it contains 20 U S P Units of insulin per cubic centimeter

Red and gray, if it contains 40 U S P Units of insulin per cubic centimeter

Green and gray, if it contains 80 U S P Units of insulin per cubic centimeter

Protamine zinc Insulin is distinguished by

Red and white, if it contains 40 U S P Units of insulin per cubic centimeter

Green and white, if it contains 80 U S P Units of insulin per cubic centimeter

Globulin zinc Insulin with zinc is distinguished by

Green and brown, containing 80 U S P units of insulin per cubic centimeter

GLOBIN INSULIN WITH ZINC—Globin insulin (with zinc) is a preparation in a hydrochloric acid medium of insulin modified by the addition of globin (derived from the hemoglobin of beef blood) and zinc chloride. The quantity of insulin used is such that each cubic centimeter of the finished product contains either 40 or 80 U S P units of insulin. The quantity of globin used (calculated as 60 times its nitrogen content) is not less than 36 mg and not more than 40 mg for

each 100 U S P units of insulin used. The preparation also contains, for each 100 U S P units of insulin used, not less than 0.25 mg and not more than 0.35 mg zinc and not more than 1.50 mg total nitrogen. The pH of the finished preparation is not less than 3.4 and not more than 3.8. If necessary, either hydrochloric acid or sodium hydroxide may be added to obtain the required pH . The finished preparation also contains not less than 1.30 and not more than 1.70 per cent (W/V) of glycerin and not less than 0.15 per cent and not more than 0.20 per cent (W/V) cresol U S P, or not less than 0.20 per cent and not more than 0.26 per cent (W/V) phenol-U S P. The preparation is sterile.—Regulations promulgated Aug. 24, 1943, by the Administrator Federal Security Agency, Certification of Batches of Drugs Composed Wholly or Partially of Insulin [8 Fed. Reg. 11837 (Aug. 27, 1943)] as amended [10 Fed. Reg. 2904-2905 (Mar. 17, 1945)].

Standards for Globin Insulin with Zinc and the Globin used in its preparation are set forth in the regulations cited.

Actions and Uses—The effects of globin insulin with zinc are essentially the same as those of insulin (which see) except that the action is intermediate between that following regular

insulin and protamine zinc insulin. The action of globin insulin with zinc is intermediate between that of regular insulin and protamine zinc insulin. It is not recommended for the treatment of diabetic coma and should never be administered intravenously. Globin insulin with zinc is quite stable but nevertheless bears on the label an expiration date for usage.

also to produce fewer local reactions on injection. It is not recommended for the treatment of diabetic coma and should never be administered intravenously. Globin insulin with zinc is quite stable but nevertheless bears on the label an expiration date for usage.

Dosage—The general principles underlying the administration of this form of insulin are the same as those governing the use of unmodified insulin. It must be administered only by deep

injection. The dosage of globin insulin with zinc may be increased slowly as needed. If the patient has been receiving protamine zinc insulin the globin insulin dosage on the first day should not exceed one half the total dose of all insulin (regular, protamine zinc) received on the previous day. On the next day the dose may be increased to two thirds of the previous total insulin dosage and then slowly adjusted as required.

may be increased slowly as needed. If the patient has been receiving protamine zinc insulin the globin insulin dosage on the first day should not exceed one half the total dose of all insulin (regular, protamine zinc) received on the previous day. On the next day the dose may be increased to two thirds of the previous total insulin dosage and then slowly adjusted as required.

BUNNELL'S WILCOX & Co., Inc.

Globin Insulin with Zinc 10 cc rubber capped vials

Globin Insulin with Zinc 10 cc Each cubic centimeter contains 40 units 0.18 per cent W/V cresol as preservative

U. S. Patent 2,161,194 (June 6, 1939 expires 1956)

INSULIN INJECTION—Insulin—Insulin Hydrochloride—An acidified aqueous solution of the active principle of the pancreas which affects the metabolism of glucose. Insulin Injection when assayed as directed shall possess a potency of not less than 95 per cent and not more than 105 per cent of the potency stated on the label and the potency shall be expressed in U. S. P. Insulin Units which are equivalent in potency to the Unit declared on the label of the container of the U. S. P. Zinc Insulin Crystals Reference Standard.

* Insulin Injection is so standardized that each cc contains either 20, 40, 80 or 100 U. S. P. Insulin Units.

The label of the Insulin Injection container must state the potency in U. S. P. Insulin Units per cc and the outside labeling of each retail package shall also state a date of expiration which must not be later than two years after the date of its removal for distribution from the manufacturer's place of storage the temperature of which shall be above 0° C but shall not exceed 15° C.

Insulin Injection must contain from 0.1 to 0.25 per cent (w/v) of either phenol or cresol. The solution must contain from 1.4 to 1.8 per cent (w/v) of glycerin. U. S. P.

For description and standards see the U. S. Pharmacopeia under Insulin Injection.

Actions and Uses—Insulin lowers the blood sugar in normal rabbits causing characteristic symptoms when a low level is reached which symptoms are overcome by the administration of dextrose. It prevents the hyperglycemia due to piqure asphyxia and epinephrine. It increases the sugar consumption of the isolated mammalian heart. It causes glycogen to be deposited in the liver of diabetic animals fed with carbohydrates and raises the respiratory quotient of such animals. It affects the metabolism of fat in diabetic animals and causes the acetone bodies to disappear from the urine. It has been demonstrated that the administration of insulin to diabetic dogs and to man in severe cases of diabetes mellitus restores temporarily to the body the impaired ability to oxidize carbohydrate and that glycogen is again stored in the liver. If a suitable dose of insulin is administered at suitable intervals to a person suffering from diabetes mellitus the blood sugar is maintained at a normal level and the urine remains free of sugar. Fat is also burned and as a result ketone bodies do not appear in the urine and diabetic acidosis and coma are prevented.

The administration of insulin is indicated in cases of diabetes mellitus which cannot be controlled at a satisfactory level by

dietetic treatment. In such cases with proper regulation of the diet insulin should be administered in such amounts as to prevent glycosuria and a too great hyperglycemia. In some cases the dosage of insulin may be gradually decreased as the body power of utilizing carbohydrate returns toward normal.

Overdosage of insulin is followed by the development of serious symptoms which demand immediate treatment. The patient complains of weakness and fatigue and a feeling of nervousness or tremulousness. This is followed by profuse sweating which is the most characteristic sign of overdosage. There is sometimes pallor or flushing. In the more severe forms there is acute distress with mental disturbances and even unconsciousness. These symptoms are relieved by the administration of some form of soluble carbohydrate such as orange juice by mouth or stomach tube or if the patient is comatose by the intravenous injection of from 5 to 20 grams

with the necessity of having adequate supplies of sterile solution of dextrose at hand. In case of emergency when sterile solution of dextrose is not available a subcutaneous injection of 0.3 cc. to 0.6 cc. of 1 in 1000 solution of epinephrine may be employed but this must always be followed by carbohydrates by mouth. The injection of epinephrine must be employed carefully as its action depends on the presence of glycogen of which there is usually very little in the diabetic organism. Epinephrine should never be employed when the hypoglycemia follows excessive exercise vomiting or the omission of meals.

Insulin has been used in the treatment of non diabetic malnutrition with reported increase in appetite and gain in weight. Care is necessary in avoiding symptoms of hypoglycemia.

Insulin has been suggested and used rather extensively in psychopathic hospitals for the purpose of producing hypoglycemic shock for its effect on the schizophrenic. It is a dangerous procedure with a relatively high mortality and should be employed only by those who are fully equipped, fully qualified and thoroughly familiar with all aspects of this method of treatment. Obviously it is essential to have available at all times suitable solutions of dextrose for interrupting the hypoglycemic state which is artificially created in these individuals by the administration of insulin.

Dosage—Insulin is administered by injection into the loose subcutaneous tissue of the body usually thirty minutes before meals. There is no average dose of insulin for diabetics, each case must be studied individually. Except when complications occur insulin is not indicated when a patient has adequate dextrose tolerance to provide him with a diet sufficient for

light work. The dose depends upon the amount of dextrose in such a diet as he is unable to metabolize, i. e. the total dextrose minus the dextrose excretion. A convenient formula

is
$$\frac{\text{Average grams of d glucose excreted}}{15} = \text{sufficient units of insulin}$$

to render most patients aglycosuric. Usually the daily dose is administered in two equal portions, one before breakfast and the other before supper. The carbohydrate of the diet should

large daily dosage
before each meal

than at the other
suric the diet can

be used to keep

the fasting blood sugar normal but hypoglycemia should be avoided. If patients are not under close observation half the estimated dose may be used and the dose gradually increased until therapeutic results are obtained. Complications such as infections may reduce the dextrose tolerance thus necessitating an increase of insulin dosage.

In cases of coma or severe acidosis an initial dose of 30-60 units may be given (in coma one half the amount intravenously and one half subcutaneously) followed at $\frac{1}{2}$ to 3 hour intervals by doses of 20 units or more subcutaneously. Some physicians administer 1 Gm of dextrose for each unit of insulin used. The patient should never become hypoglycemic. Examine the urine hourly for dextrose. If urine becomes sugar free more dextrose must be given. More than 150 units of insulin in twelve hours is rarely needed. Young children with diabetes of recent onset usually require smaller doses and seldom more than 80 units in the first 12 hours.

In a small number of cases of diabetes mellitus insulin can be discontinued particularly with patients who receive it because of an exacerbation caused by complications and where diabetes is of recent onset (though perhaps the latter should receive it intermittently as a prophylactic against increasing severity).

Dosage of insulin should always be expressed in units rather than in cubic centimeters or minims. The volume of a dose of insulin containing a certain number of units will vary with the strength of the solution which is employed. In general it is advisable to keep the volume per injection at from $\frac{1}{4}$ to $\frac{3}{4}$ cc choosing the strength of insulin which will give the required number of units in this volume or less.

U S patents 1 469 994 (Oct. 9 1923 exp red) 1 470 024 (Oct. 9 1923 exp red) and 1 520 673 (Dec. 23 1924 exp red) Canadian patent 234 336 and 234 337 U S trademark 179 174 Canadian trade mark 31 646

ELI LILLY AND COMPANY

letin U 20 U 40 U 80 and P 100 10 cc vials. Each 1 cc contains 20 40 80 and 100 units insulin respectively.

U S trademark 171 971

SHARP & DOHME, INC.

Insulin: 20 units, 40 units, 80 units, 100 units · 10 cc. vials
Each 1 cc contains 20, 40, 80 and 100 units respectively

Beef pancreas is rendered as free from fat and connective tissue as possible, and extracted with acidulated 60 per cent alcohol. The mixture is centrifugalized and the gland residue reextracted with 60 per cent alcohol. The alcoholic liquid is then concentrated to about one twelfth its original volume. The active substance is then precipitated with ammonium sulfate and reprecipitated from an alcoholic solution. It is further purified by a method of isoelectric precipitation and is finally dissolved in acid water (pH 2.5). 0.25 per cent phenol is used as preservative and glycerin 1.6 per cent is added in order to attain isotonicity. It is then filtered through a Berkefeld filter and submitted to sterility tests, its potency is determined by the method described under the preceding article, *Insulin*.

E. R. SQUIBB & SONS

Insulin, 20 units 40 units, 80 units, 100 units 10 cc vials
Each 1 cc. contains 20, 40, 80 and 100 units respectively

Insulin Squibb is made by extracting finely ground beef pancreas with acidulated aqueous alcohol and subsequently removing the tissue

Fresh pancreatic glands of animals, from which fat and connective tissue have been removed are ground and extracted with 1½ volumes 95 per cent alcohol, containing 0.11 per cent absolute sulfuric acid. The mixture is agitated during two hours and then filtered. The residue is again extracted using an equal volume of 70 per cent alcohol containing 0.11 per cent absolute sulfuric acid. This is filtered and the filtrate added to the first filtrate. The combined

PROTAMINE ZINC INSULIN.—A preparation of insulin modified by appropriate addition of protamine and a zinc salt. When this modified preparation in its precipitated form is contained in a glass ampoule of 1 cc. capacity, it contains 4 to 0.6 mg. of insulin. The preparation is stable for a period of 6 months. The preparation is used in the treatment of diabetes mellitus. The preparation is used in the treatment of diabetes mellitus.

maintain its hydrogen ion concentration at not more than that corresponding to $pH=7.1$ and not less than that corresponding to $pH=7.4$. This buffering agent, in terms of its anhydrous salt (Na_2HPO_4), represents not less than 0.15 per cent and not more than 0.25 per cent of the final product. The preparation also contains approximately 1.6 per cent of glycerin as an agent for achieving isotonicity, and 0.20 per cent of cresol or 0.25 per cent of phenol as a preservative.

For diabetics who require larger single doses, protamine zinc insulin is prepared in a form which contains 80 units per cc. Since there is some individual variation in the rate of absorption of protamine zinc insulin, the danger of inducing severe hypoglycemia must be considered when large doses are given to patients who are not accustomed to receive their daily requirement in a single injection.

Actions and Uses—The effects of protamine zinc insulin are the same as those of Insulin (which see), except that the blood sugar lowering action of unmodified insulin becomes maximal in from two to three hours, whereas the blood sugar-lowering

patient. In some cases the use of unmodified insulin alone is desirable, in others, protamine zinc insulin alone is indicated, while in others, the use of both preparations gives best results.

In view of the prolonged action of protamine zinc insulin, the chief indications for its use are in those cases where unmodified insulin is unable to provide control, without being administered in several doses daily, or is unable to provide adequate control una-

tions, ketosis, or eyi-

sugar levels. The u-

of diabetic coma, in

event of surgical operations has not been definitely established.

In such instances, therefore, the use of protamine zinc insulin to supplant the use of unmodified insulin is not recommended.

Dosage—The general principles underlying the administration of protamine zinc insulin are the same as those governing the administration of unmodified insulin (see Insulin N N R).

Protamine zinc insulin is to be injected *only subcutaneously*. In most cases its administration more often than once a day is not required. The initial dose should be from about two-thirds to equal the number of units that would be needed daily to maintain the patient "sugar free" under treatment with unmodified insulin. In some instances glycosuria may follow owing to the slow absorption and consequent delayed action of protamine zinc insulin. Hence on the first few days when

protamine zinc insulin is being used it may be advantageous to administer a separate dose of unmodified insulin. It is usually possible to discontinue the use of unmodified insulin after the first or second day, though in some instances the administration of both preparations requires to be continued indefinitely.

Protamine zinc insulin is generally administered either in the morning (from one half to one and one half hours before breakfast), or in the evening (one hour before supper or one hour before retiring). Diet must be adjusted with the prolonged blood sugar lowering effect of the product in mind and a redistribution of food among individual meals is usually desirable. In particular, the carbohydrate content of the meal following the injection of protamine zinc insulin may require to be limited in order to avoid *hyperglycemia*. The carbohydrate of the diet not included in this meal is divided between the other meals of the day in such a manner as to prevent *hypoglycemia* at times when the dose of protamine zinc insulin is exerting its greatest effect.

prolonged, and despite its having been treated it may repeat itself owing to the continuing effect of the dose administered. It is therefore advisable to use both a soluble and a more slowly digestible carbohydrate in treating such reactions for example corn syrup with bread or bread with honey. Alternatively, and even though the patient may *appear* to be restored to normal through use of a soluble carbohydrate food such as orange juice it is advisable to provide additional carbohydrate after the lapse of one or two hours. Soda biscuits and milk are suitable at that time. In severe reactions, it may be desirable to inject from 15 to 20 Gm. of dextrose in sterile solution intravenously followed later by food.

In protamine zinc insulin the insulin component is derived from batches previously tested and approved in their unmodified form, the protamine component is derived from sperm or mature testes of fish belonging to the family Salmonidae genus *Oncorhynchus*, *Salmo* or *Trutta* and the zinc component is derived from a solution of zinc chloride (0.17 mg. of $ZnCl_2$ provides 0.03 mg. of zinc). Protamines are basic proteins of simple composition. These substances are pre-

is tested by comparison with protamine zinc insulin reference material specified by the Food and Drug Administration. The sample under test is considered satisfactory only if, upon comparison by suitable methods of biological assay, its effects are shown to be essentially the same as the effects given by the other sample.

To estimate its zinc content, transfer about 1 cc accurately measured, of the well mixed protamine zinc insulin to a 25 cc platinum dish, add 0.3 cc of 1:1 mixture of sulfuric acid and water, evaporate and ignite residue slowly (begin with the muffle door open, then increase the heat to around 650° with the door closed). After ashing cool, add 15 cc of water and 7 cc of 3 normal hydrochloric acid. Evaporate the solution to one-half volume on the steam bath and filter into a 50 cc Erlenmeyer flask. Wash the residue until the volume of the filtrate is approximately 25 cc, add 3 drops of solution of bromphenol blue, followed by stronger ammonia water until the solution assumes a blue color, then add just enough hydrochloric acid to make the solution slightly yellow. Add approximately 5 cc of sodium citrate buffer (12 Gm sodium citrate, 23 Gm citric acid in 100 cc water) and adjust the entire mixture to a $\text{pH} \approx 3.0$. The solution should now have a gray color—neither yellow nor blue. Warm the solution on a steam bath and rapidly pass in hydrogen sulfide for two minutes. (Iron may be reduced in slightly acid solution by using a little SO_2 .) Add 0.05 Gm of acid and alkali washed talcum. Filter the solution through a Whatman filter No. 1 (7 cm), wash with 10 cc hydrogen sulfide saturated water containing 5 cc of 90 per cent formic acid in 1 liter. After the filter is dry, elute the zinc with approximately 15 cc 1 normal hydrochloric acid and transfer into a flat bottom Nessler tube. Add 2 cc of 5 normal sodium hydroxide and fill up to 20 cc. Add 2 drops of 2 per cent potassium ferrocyanide and compare with standards containing 0.05 mg to 0.1 mg zinc (nephelometrically). One cc of protamine zinc insulin containing 40 units per 1 cc should yield the equivalent of not less than 0.05 mg, nor more than 0.10 mg of zinc. The zinc standard is made by dissolving 1 Gm of pure zinc in concentrated hydrochloric acid, diluting it to 1 liter.

Patents and trademarks.—See Insulin N N R

ELI LILLY AND COMPANY

Protamine, Zinc and Iletin, 40 Units and 80 Units: 10 cc vials. Each 1 cc contains 40 and 80 units of protamine zinc insulin respectively.

SHARP & DOHME, INC.

Protamine Zinc Insulin, 40 Units and 80 Units: 10 cc vials. Each 1 cc contains 40 and 80 units of protamine zinc insulin respectively. Contains disodium acid phosphate 0.2 per cent, phenol 0.25 per cent as a preservative, and glycerin 1.6 per cent for isotonicity.

E. R. SQUIBB & SONS

Protamine Zinc Insulin, 40 Units and 80 Units: 10 cc vials. Each 1 cc contains 40 and 80 units of protamine zinc insulin respectively.

ZINC INSULIN CRYSTALS.—Zinc insulin crystals occur as a crystalline preparation of the active antidiabetic principle of the internal secretion of the islands of Langerhans.

of the pancreas. The crystals contain a small amount of zinc (not less than 0.45 per cent and not more than 0.9 per cent) which is chemically combined with the active principle. Each milligram of the crystals is equivalent to not less than 22 units of insulin. The product is marketed in the form of crystalline zinc insulin injection.

Zinc insulin crystals occur as small colorless crystals which exhibit the following optical properties: uniaxial positive, habit flat rhombohedra, with slightly rounded edges commonly in dual sometimes in multiple growths along the C axis resembling twinning clear and colorless elongation of the flat rhombohedra is negative, refractive indices $n = 1.536$ $w = 1.545$. It is sparingly soluble in water insoluble in alcohol chloroform and ether but soluble in dilute acid and dilute alkali. The isoelectric point of zinc insulin crystals is about 5.3. The crystals are stable if kept at a low temperature.

Transfer to a microscope slide approximately 0.1 mg. of zinc insulin crystals add 0.1 cc. of distilled water, thoroughly wet the crystals by

Transfer about 20 mg. of zinc insulin crystals to a platinum boat weigh the boat and its contents within a weighing pig place the boat in a vacuum desiccator over phosphorus pentoxide and dry to constant weight using the weighing pig to prevent the absorption of water during weighing. The loss in weight does not exceed 7.0 per cent. In the following quantitative determinations it is more convenient to weigh the zinc insulin crystals directly and to calculate the results to a dry basis rather than attempt to weigh the extremely hygroscopic dry material.

Dissolve 50 mg. of zinc insulin crystals in 5 cc. of water by the addition of sufficient tenth normal hydrochloric acid to effect solution transfer to a centrifuge tube and add 2 cc. of 10 per cent trichloroacetic acid with shaking let stand ten minutes and centrifuge decant into a 10 cc. volumetric flask add 2 cc. of Nessler's reagent and make up to volume allow to stand five minutes transfer to a colorimeter and compare with a standard made up similarly and containing 0.035 mg. of ammonium sulfate the color does not exceed that of the standard solution.

chloroform is no longer colored pink. At this point the aqueous layer may be discarded. Transfer the combined chloroform extracts to a clean separator and extract twice with 15 cc. portions of 0.02 normal

0.45 per cent nor more than 0.9 per cent (An alternative method for the determination of zinc content is provided in the U. S. P. XII under Zinc in Insulin Injection.)

Transfer about 10 mg. of zinc insulin crystals to a platinum dish, add two drops of concentrated sulfuric acid, ash slowly and ignite to constant weight at 600 C. the ash is not more than 50 per cent more than the zinc sulfate calculated from the zinc content and in no case is it more than 3.30 per cent.

CRYSTALLINE ZINC INSULIN INJECTION—

Insulin Made from Zinc Insulin Crystals—A solution of zinc insulin crystals, a preparation containing the active antidiabetic principle of the pancreas combined with a small amount of zinc (not less than 0.2 and not more than 0.40 mg. per thousand units of active principle in the solution).

Crystalline zinc insulin injection meets the requirements for identity and purity provided in the U. S. P. XII under Injection Insulin.

Actions and Uses—Crystalline zinc insulin injection may be used in the treatment of diabetes mellitus when regulation of diet has been unsatisfactory in control of the disease. Because of its chemical purity, solution of zinc insulin crystals is especially indicated for patients who may be expected to exhibit allergic reactions to insulin. Experience has indicated that the occurrence of such reactions may thus be avoided or minimized. Although early clinical observations indicated that the action of crystalline zinc insulin injection as compared with that of insulin may be slightly delayed and somewhat prolonged, further clinical experience has shown, however, that in patients under careful observation crystalline zinc insulin injection and insulin may be used interchangeably.

Dosage—The potency of crystalline zinc insulin injection is measured in terms of standard units of insulin. The general principles underlying its administration are the same as those covering the use of insulin and under ordinary circumstances the two solutions may be regarded as interchangeable. The crystalline zinc insulin injection is usually best administered subcutaneously fifteen to thirty minutes before a meal. The time and number of the doses and the amount of solution must be determined by the need of the individual patient, each of whom requires accurate dietary regulation and meticulous clinical study.

Marketed solutions of zinc insulin crystals are water clear and contain from 1.4 to 1.8 per cent w/v of glycerin for isotonicity, 0.1 to 0.25 per cent w/v of phenol or tricresol as a preservative and sufficient 0.01 normal hydrochloric acid to yield a pH of from 2.5 to 3.5. The biologic activity of the solution is expressed in U. S. P. insulin units per cubic centimeter. Solutions of zinc insulin crystals are stable provided the storage temperature does not exceed room temperature.

Parathyroid

Parathyroid preparations for oral administration are made from the dried gland and for subcutaneous administration by extraction of the gland by suitable solvents and subsequent purification of the product. The reports of success after oral therapy lack any conclusive evidence that this was dependent upon the use of the gland. No proof has been brought forward that the one definite effect that can be referred to the parathyroid gland (maintaining or raising the calcium concentration of the serum) has been produced by parathyroid preparations

preparations of parathyroid designed for oral administration are not accepted for inclusion in this book.

Preparations which have a powerful influence on calcium metabolism may be made from the parathyroids of the ox. If this substance is injected intramuscularly or subcutaneously the calcium concentration of the serum of animals deprived of their parathyroid glands can be raised and maintained at a normal limit. By repeated doses it may be raised far beyond this, either to a level which is fatal to the animal, and unless the preparation is carefully controlled. The raising of the calcium concentration of the serum in animals or in normal animals. On subcutaneous and intramuscular injections the plasma calcium begins to rise in about 4 hours, reaches its maximum in from 12 to 18 hours and returns to the previous level in from 20 to 24 hours. Associated with the rise in serum calcium is an increased urinary excretion of calcium and inorganic phosphate and a decrease in the serum content of the latter. An immunity or tolerance to the hormone is induced by repeated administration. Treatment by these parathyroid preparations has been shown to be of value in tetania parathyreopriva. In infantile tetany their employment should be confined to those cases in which a reduction in the level of serum calcium has been demonstrated and would appear to be a temporary expedient until other measures have an opportunity to combat the fundamental underlying condition. In gastric tetania the calcium of the serum is normal and there has been

hypercalcemia, which is easily induced by overdosage and which is associated with grave manifestations, makes it desirable that the clinical use of parathyroid preparations should be controlled by blood serum calcium determinations or by applica-

tion of the Sulkowitch test for calcium in the urine. The normal concentration of calcium in human serum being approximately 10 mgm of calcium per 100 cc of serum, values above 12 mgm are considered undesirable while those above 15 mgm may be dangerous. Injections of parathyroid solutions may produce troublesome local reactions, which interfere with their continued use. Repeated doses may establish tolerance to the hormone, with almost complete loss of therapeutic effect. For this reason, other substances, such as dihydrotachysterol or calciferol, which cause elevation of serum calcium, should be substituted as soon as possible.

PARATHYROID INJECTION—Parathyroid Extract—*Solution of Parathyroid*—“A sterile solution in water for injection of the water soluble principle or principles of the parathyroid glands which have the property of relieving the symptoms of parathyroid tetany and of increasing the calcium content of the blood serum in man and other animals. It is obtained from the fresh parathyroid glands of healthy domesticated animals used for food by man, the animal source of each preparation being stated. The parathyroid glands must be removed from the animals immediately after slaughtering, and then extracted at once or kept frozen until extracted. The glands are freed from gross fat and connective tissue, ground, extracted, and the extract purified to make it suitable for parenteral administration. The injection is then adjusted to the proper potency.

‘One cc of Parathyroid Injection possesses a potency of not less than 100 U S P parathyroid units, each unit representing one one hundredth of the amount required to raise the calcium content of 100 cc of the blood serum of normal dogs 1 mg within sixteen to eighteen hours after administration’
U S P

For description and standards see the U S Pharmacopeia under Parathyroid Injection.

Actions and Uses (See preceding article Parathyroid)

Dosage—In severe seizures of acute proved parathyroid tetany such as may follow removal of the parathyroid glands during thyroidectomy a dose of 100-300 units (10-30 cc) may be necessary. Beneficial effect, as evidenced by an elevation in the serum calcium, is usually apparent within a few hours and reaches a maximum in 8-18 hours. For maintenance of the level of serum calcium the average adult dose is 0.2-0.4 cc (20-40 units) every 12 hours. The continuance and regulation of such dosage must be controlled by determinations of the level of the serum calcium. In the treatment of chronic parathyroid tetany parathyroid injection is less effective than dihydrotachysterol or vitamin D₂ and is usually unnecessary if

one of these substances can be provided in appropriate amounts. In infants the use of parathyroid injection should be more cautious and even in those cases where a reduction of serum calcium has been demonstrated the initial dosage should not exceed 0.1-0.2 cc (10-20 units).

ELI LILLY AND COMPANY

Solution Parathyroid Extract 1 cc ampuls and 5 cc vials
Each 1 cc contains 100 units

PARKE, DAVIS & COMPANY

Solution Paroidin 5 cc vials Each 1 cc contains 100 units

U S patent 1 890 851 (Dec 13 1932 exp res 1949) U S trademark

E. R. SQUIBB & SONS

Solution Parathyroid Hormone 5 cc vials Each cc contains 100 units

Pituitary

Posterior Lobe—The posterior lobe of the pituitary gland yields on extraction substances having a marked effect on plain muscle, especially that of the blood vessels and the uterus. The intravenous or intramuscular injection of preparations of the posterior lobe is sometimes followed by an increase in blood pressure which is maintained over a considerable period of time. Injection of subsequent doses in such cases is followed by a similar effect unless repeated too soon after the first injection, when a fall in pressure may occur. The increase in pressure is due to an action on the smooth muscle of the vessels. In a considerable number of individuals the increase in blood pressure may be very slight and in some instances instead of an increase a definite lowering of the blood pressure may follow the injection of pituitary preparations. The heart is not stimulated in any case and may be depressed either through the vagus response to a high blood pressure or by a direct action on the heart muscle itself or through impairment of its nutrition because of constriction of the coronary vessels. The tone of the intestinal tract may be markedly increased by direct action on the muscular coat. The administration of extracts usually retards the secretion of urine to a marked degree during the first hour and a half and sometimes longer. There is some experimental evidence to show that the absorption of water from the gastrointestinal tract is delayed thereby lessening the water available for secretion. However, the antidiuretic action may be due to increased reabsorption of water from the kidney tubules into the blood.

The bladder musculature is stimulated especially when it has been previously in an atonic condition. Posterior pituitary extract does not increase the formation of milk but may cause a temporary acceleration of the output. The extract of the posterior lobe causes a marked contraction of the uterus by a direct stimulating action on the muscle. This occurs especially in pregnant and to a less extent in nonpregnant animals.

Solutions prepared from the posterior lobe injected intramuscularly are employed against uterine atony and in postpartum as well as in other forms of uterine hemorrhage. They should not be injected during the first stage of labor because if the cervix be not fully dilated energetic contractions may cause rupture of the uterus or extensive laceration of the soft tissue. Most authorities also advise against the use of pituitary preparations in the second stage of labor.

Pituitary solutions may be useful in intestinal paresis whether following abdominal operations or complicating infectious diseases. The extracts are also extensively used in diabetes insipidus in which they reduce greatly the volume of urine excreted. For this purpose they are injected once or twice daily. The extracts should always be injected hypodermically or intramuscularly although some activity appears when they are applied to the nasal mucous membrane. The extract of the posterior lobe of the pituitary gland has been fractionated: one product (pitocin) acting on the uterus and a second product (pitressin) producing the characteristic effect of the original solution on the blood vessels, intestine and urinary secretion.

Anterior Lobe—Hyperactivity of the anterior lobe is believed to produce gigantism and acromegaly, for clinically both conditions have been accompanied by tumors of the pituitary. Evidence has accumulated which indicates that the hormone of the anterior lobe is essential to normal growth and the development of the ovaries and testes but that it may have nothing to do with some of the other disturbances formerly attributed to abnormal function of the anterior lobe.

of cases of F
the pituitary
that extirpation of the hypophysis in adult dogs and white rats without injury to the hypothalamus does not produce dystrophia adiposogenitalis. Extirpation in immature animals is followed by cessation of growth and sexual development, a condition which has been corrected in white rats by daily transplants of the anterior lobe of the pituitary or by daily injections of appropriate amounts of the fresh extract of the anterior lobe of bovine glands.

Present evidence would seem to indicate that a number of factors are concerned in the action of extracts of the anterior lobe: (1) a growth factor concerned with the development of the body; (2) a factor which stimulates the growth and matu-

ration of the ovarian follicle, which in turn bring on the changes characteristic of estrus, (3) a factor which causes luteinization of the ovarian follicles, (4) a factor which is necessary for normal thyroid development and function and which, if present in excess, produces hyperplasia of the thyroid with hyperthyroidism in both the rat and the guinea pig, (5) a factor which produces lactation in mammals and possibly

thus producing the diabetic syndrome, and (7) a ketogenic principle, apparently distinct from the diabetogenic factor, which increases the ketone content of the blood in rabbits and rats. In addition to the above enumerated factors the existence of which seems to be clearly established experimental evidence has been offered indicating the presence of other principles among these is one which stimulates the adrenal cortex known as the adrenotropic hormone.

A gonadotropic substance which forms the basis of pregnancy tests occurs in large amounts in the urine of pregnancy. Although this substance was originally considered to come from the anterior pituitary gland the placenta which also yields it in large amounts seems to be a more probable source. It is predominantly luteinizing in action in contrast to the anterior lobe principle found in the urine at the menopause and after castration which produces a greater degree of follicular stimulation.

The Council believes that extensive clinical trial has failed to establish the value of desiccated pituitary preparations for oral administration whether these are prepared from the anterior or from the posterior lobe.

AMPULS PITOCIN—An aqueous solution containing the oxytocic principle of the posterior lobe of the pituitary gland (alphahypophamine) containing less than $\frac{1}{2}$ unit of pressor activity per cubic centimeter. Five tenths per cent of chlorbutanol is used as a preservative. It is standardized by the U S P method for posterior pituitary each cubic centimeter containing 10 units. Pitocin therefore has an activity on the uterus equal to that of the U S P solution of pituitary.

Actions and Uses—Pitocin is used to stimulate uterine contractions in obstetrical practice.

Dosage—From 0.3 cc to 1 cc intramuscularly. If used before delivery is completed small doses are used repeated if necessary in twenty to thirty minutes.

PARKE, DAVIS & COMPANY**Pitocin** 0.5 cc and 1 cc ampuls

U S patent 1,960,493 (May 29, 1934 expires 1951) U S trade mark 254 956

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20 pressor units (1 unit represents the pressor activity exhibited by 0.5 mg of Posterior Pituitary U S P Reference Standard U S P) It has, therefore, twice the pressor potency of Posterior Pituitary Injection U S P

Actions and Uses—Pitressin is used for raising the blood pressure, for increasing the muscular activity of the bladder and intestinal tract, also for antidiuretic effect in diabetes insipidus (See preceding article, Pituitary)

Experimental evidence has been obtained indicating that the product increases the blood sugar and it has been successfully employed to counteract overdoses of insulin in animals. No clinical studies to determine the value for this purpose have been reported so far. It has been suggested that the product may be of value either in conjunction with or supplementary to the use of epinephrine in the treatment of serum sickness and similar vasomotor disturbances, but no definite evidence on this point is as yet available.

Dosage—From 0.3 to 1 cc intramuscularly, repeated as may be indicated.**PARKE, DAVIS & COMPANY****Pitressin** 0.5 cc and 1 cc ampuls

U S patent 1,960,493 (May 29, 1934 expires 1951) U S trade mark 254 507

PITRESSIN TANNATE IN OIL—A suspension in vegetable oil of a water insoluble tannate of the pressor and diuretic antidiuretic principle of the posterior lobe of the pituitary gland (beta hypophammine) standardized to contain five pressor units in each cubic centimeter (one unit representing the pressor activity exhibited by 0.5 mg of standard powdered pituitary U S P). It is standardized by the method of Hamilton and Rowe (*J Lab & Clin Med* 2:120 [Nov] 1916).*Actions and Uses*—Pitressin tannate in oil is recommended for use where the prolonged action of pitressin is desired particularly for the treatment of patients suffering from diabetes insipidus.

Dosage—1 rom 0.3 to 1 cc (3 to 5 pressor units) intramuscularly *not intravenously* at intervals of from thirty six to forty eight hours

PARKE DAVIS & COMPANY

Pitressin Tannate in Oil 1 cc ampuls Each cubic centimeter contains pitressin tannate equivalent to 5 pressor units in peanut oil suspension

U. S. patent 1,960,493 (May 29, 1934 expires 1951) U. S. trade mark 254,507

POSTERIOR PITUITARY INJECTION—Liquor Pituitarii Posterioris U. S. P. XI—Solution of Pituitary—A sterile solution in water for injection of the water soluble principle or principles from the fresh posterior lobe of the pituitary body of healthy domesticated animals used for food by man. The pituitary body must have been removed from the animal immediately after slaughtering and then dried or extracted at once or kept frozen until extracted. The potency of Posterior Pituitary Injection shall be such that 0.1 cc of the Injection shall possess an activity equivalent to one U. S. P. Posterior Pituitary Unit U. S. P.

For description and standards see the U. S. Pharmacopeia under Posterior Pituitary Injection

Actions and Uses—See preceding article Pituitary

Dosage—For use in obstetrical cases from 0.2 to 1 cc in surgical cases from 1 to 2 cc preferably by deep intramuscular injection or subcutaneously

ABBOTT LABORATORIES

Posterior Pituitary Injection 0.5 cc and 1 cc ampuls

THE ARMOUR LABORATORIES

Pituitary Liquid 0.5 cc and 1.0 cc ampuls

ENDO PRODUCTS, INC.

Solution of Posterior Pituitary 0.5 cc and 1 cc ampuls

LAKESIDE LABORATORIES, INC.

Pituitary Solution 1 cc ampuls

Pituitary Solution 10 cc and 30 cc vials

ELI LILLY AND COMPANY

Pituitary Extract 0.5 cc and 1 cc ampuls

THE W. S. MERRILL COMPANY (FORMER LABORATORY DIVISION)

Pituitary Extract

PARKE, DAVIS & COMPANY

Pituitrin 0.5 cc and 1 cc ampuls

U. S. trademark 76 722

F. R. SQUIBB & SONS

Posterior Pituitary Injection 0.5 cc and 1 cc ampuls

THE UNION COMPANY

Posterior Pituitary Injection 0.5 cc and 1 cc ampuls

Posterior Pituitary Injection 20 cc vials

U. S. STANDARD PRODUCTS CO.

Pituitary Solution 0.5 cc and 1 cc ampuls

Pituitary Solution 10 cc and 30 cc vials

WILLIAM R. WARNER & CO., INC.

Posterior Pituitary 1 cc ampuls

WARREN TIED PRODUCTS COMPANY

Posterior Pituitary Injection 10 cc rubber capped vials

THE WILSON LABORATORIES

Solution Posterior Pituitary Contains chlorobutanol 0.5 per cent as a preservative

Placenta

Gonadotropic Substances

Three types of biological substance which stimulate the gonads of either sex are to be distinguished. The fundamental physiological gonadotropic hormone of the normal animal body is produced by the anterior pituitary. The chemical nature of this material is unknown and there is still debate as to whether there are one, two, or more pituitary gonadotropic hormones.

The serum of the pregnant mare contains a gonadotropic substance which acts in a manner very similar to the preparations made from the anterior lobe. This substance is susceptible of refinement to a point where very little inert protein accompanies the active gonadotropic substance. It is probable that only one active compound is involved. An international unit of this substance has been defined by the special committee of the League of Nations by comparison with a dry powder preparation supposed to be of stable potency. No preparation of this material is accepted by the Council.

The blood serum of pregnant women contains a gonadotropic substance which is distinct from that in the serum of the pregnant mare in several respects. The latter substance does not pass out into the maternal blood in appreciable amounts, whereas the serum of pregnant women contains a distinct amount of the hormone, which is termed chorionic gonadotropin substance.

In studies in respect to pregnancy serum, certain extracts thereof, which are called chorionic gonadotropin, have been formed. When the gonadotropic activity of pregnancy serum was first demonstrated by Zondek, it was concluded that the responsible substance was secreted by the anterior pituitary. At the time, the concept was advanced that this gonadotropic extract consisted of two distinct principles, the follicle stimulating hormone, and prolactin. The following experiments, the last of its effect on the rat, mouse and rabbit. Further experimentation, however, has revealed that this substance is a single entity and not composed of two factors, that it arises from the placenta rather than from the pituitary, and that it differs fundamentally from the gonadotropins of the anterior pituitary.

A significant physiological difference between chorionic gonadotropin and preparations from the anterior pituitary is the inability of the former to stimulate to any appreciable extent the ovary of the monkey or the human being. In case of chorionic gonadotropin, primates will not induce follicular growth or corpus luteum formation. On the contrary, reliable investigations have observed definite degenerative changes in the ovaries of women and monkeys treated with this substance. In addition, no clearest endometrial responses have been observed in primates treated in this manner, which indicates conclusively the inability of this substance to stimulate the growth of normal ovarian structures.

The physiological action of chorionic gonadotropin is not limited to the female, but it exerts a definite effect on the male reproductive organs. It is generally agreed that this substance acts on the interstitial cells of the testes, causing them to elaborate the androgenic hormone of the testis, which in turn induces growth of the accessory sex organs. This substance is effective in male monkeys and human beings. Among the reactions induced in the monkey is the descent of the testes in the prepubertal animal. In some animals there may be some increase in the size of the seminiferous tubules, but there is little if any effect on the germinal epithelium. Spermatogenesis is, however, maintained by chorionic gonadotropin in recently hypophysectomized rats, but it is not restored after atrophy or induced in normal immature rats.

The therapeutic application of chorionic gonadotropin has covered a wide range of conditions. Many of the trials have been on an unsound or improperly conceived basis. Its use in

the treatment of ovarian disturbance, for example, has no scientific rationale at the present time, although when it was first introduced for the treatment of these dysfunctions the physiological basis for therapy appeared excellent

CHORIONIC GONADOTROPIN — Follutein — Koro-trin — The water soluble gonadotropic substance obtained from the urine of pregnant women. It is a glycoprotein containing about 12 per cent of galactose. This preparation is standardized in international units. One international unit equals 0.1 milligram of a standardized powder (see Council Report, *J A M A* 113:2418 [Dec. 30] 1939).

Actions and Uses — Its use is recommended in the treatment of cryptorchidism where there are no anatomic lesions causing obstruction of the testicular descent. The diagnosis of an anatomic lesion can often be made in this manner where this therapy fails. Thus the surgical treatment of cryptorchidism may be instituted at an early age when it is found that hormone therapy cannot induce descent. Injections should not be prolonged after six to eight weeks if no descent is obtained since excessive therapy may result in undesirable responses of precocious puberty and possibly other harmful reactions.

The diagnosis of cryptorchidism should not include those cases which have been termed *pseudocryptorchids* in which the testes are maintained in the inguinal canal as the result of reflex muscular spasm. It will be found that the testes return to the normal scrotal position on gentle handling and warmth.

Chorionic gonadotropin therapy in other disorders is still considered experimental because of the lack of convincing data. The treatment of hypogonadism in the adult is considered experimental at the present time. Its value in the treatment of uterine bleeding of functional nature is also as yet unproved although numerous reports on this therapy have appeared in scientific publications. There is less enthusiasm for this therapy at the present time than there was several years ago. Considerable disagreement exists among the various investigators regarding the type of bleeding benefited by chorionic gonadotropin therapy.

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descent. Therapy should be discontinued on the development of signs of precocious maturity.

Preparation —

Chorionic gonadotropin is prepared from the urine of normal pregnant women by precipitating the active principle from the urine by addition of ethyl alcohol to give a concentration of more than 85 per cent alcohol extracting the hormone from the precipitate with dilute alkaline water and then salting out the active principle from this solution with

ammonium sulfate. Further purification is made by fractionating in 50 per cent alcohol at the isoelectric point of impurities, which are removed by centrifuging. The active principle is obtained by raising

of the International Standard

GEORGE A. BREON & CO., INC.

Chorionic Gonadotropin, 1,000 and 5,000 International Units, 10 cc. vials. A powdered preparation of chorionic gonadotropin packaged in vials which, when treated with the accompanying 10 cc of phosphate buffer solution, furnishes solutions having a potency of 100 and 500 international units per cubic centimeter, respectively.

SHARP & DOHME, INC.

'Lyovac' Chorionic Gonadotropin, 500 International Units, 5 cc. A powdered preparation which when diluted with the accompanying 5 cc of sterile distilled water containing 0.35 per cent of phenol, provides a solution having a potency of 100 international units per cubic centimeter.

'Lyovac' Chorionic Gonadotropin, 1,000 International Units, 10 cc. A powdered preparation which when diluted with the accompanying 10 cc of sterile distilled water containing 0.35 per cent of phenol provides a solution having a potency of 100 international units per cubic centimeter.

'Lyovac' Chorionic Gonadotropin, 2,500 International Units, 5 cc. A powdered preparation which when diluted with the accompanying 5 cc of sterile distilled water containing 0.35 per cent of phenol provides a solution having a potency of 500 international units per cubic centimeter.

E. R. SQUIBB & SONS

Follutein (Powder)

Follutein, 1,000 International Units, 5,000 International Units and 10,000 International Units. Vials containing a powdered preparation of chorionic gonadotropin which when diluted with the accompanying 10 cc of sterile distilled water containing 0.5 per cent of phenol, provides a solution having a potency of 100, 500 and 1,000 international units per cubic centimeter respectively.

Manufactured by license under U. S. patent 1,910,298

WINTHROP CHEMICAL COMPANY, INC.

Korotrin 100 International Units, 500 International Units, 1,000 International Units and 5,000 International Units. 100 and 500 international units supplied in 2 cc ampuls.

A powdered preparation of chorionic gonadotropin admixed with sucrose which when diluted with the accompanying 2 cc of sterile distilled water containing 0.2 per cent of metacresol provides a solution having a potency of 50 international units or 250 international units per cubic centimeter respectively. Marketed in boxes of 5 ampuls with 5 ampuls korotrin diluent and in boxes of 25 ampuls without diluent. 1000 international units supplied in 10 cc vials. A powdered preparation of chorionic gonadotropin admixed with sucrose which when diluted with the accompanying 10 cc of sterile distilled water containing 0.2 per cent of metacresol provides a solution having a potency of 100 international units per cubic centimeter. Marketed in packages containing 1 or 10 vials with 1 or 10 bottles korotrin diluent. 5000 international units supplied in 10 cc vials. A powdered preparation of chorionic gonadotropin admixed with sucrose which when diluted with suitable amounts of the accompanying 50 cc of sterile distilled water containing 0.2 per cent metacresol provides solutions having a potency of 100 or 500 international units per cubic centimeter. Marketed in packages containing 1 vial with 1 bottle of korotrin diluent.

Testes

Testosterone or testicular hormone has been isolated from testicular tissue and is said to be secreted by the interstitial cells. It is responsible for the development and maintenance of the accessory male organs and characteristics. Following castration in the male seminal vesicles, prostate and penis undergo severe atrophy. Libido is diminished and sexual activity is depressed. Injections of testosterone will restore these structures and functions to normal. They undergo regression however following cessation of injections. Testosterone propionate is the most effective available androgen for clinical use, the efficiency of testosterone being increased through delaying absorption from the site of injection by combination with propionic acid. Testosterone is effective by percutaneous administration. Methyl testosterone, a synthetic derivative, is much more active than testosterone when given orally. The physiological action is similar. Testosterone is not excreted in the urine and should not be confused with the urinary androgens.

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promise in the replacement therapy of eunuchoidism but many other claims made by promoters are unwarranted or are still in the experimental stage. The beneficial effects in treating castrates or eunuchoids are present only as long as injections are continued. The cost of treatment in the appropriate doses is offset by the beneficial effect in psychic impotence or disability of symptoms due to

prostatism has been claimed following treatment with this substance but substantial evidence in this regard is lacking. Recent reports indicate that in adequate doses this androgen is effective in treating certain ovarian dysfunctions such as menorrhagia and dysmenorrhea. Therapy in these instances is still experimental and there has been reported the induction of significant degrees of virilism in women when the amounts of androgen administered were considerable (350-400 mg per month). Neither testosterone nor any preparation of it stands accepted by the Council.

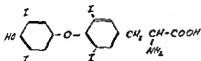
Thyroid

THYROID—'The cleaned, dried and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by man.

Thyroid contains not less than 0.17 per cent and not more than 0.23 per cent of iodine in thyroid combination, and must be free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. A desiccated thyroid of a higher iodine content may be brought to this standard by admixture with a desiccated thyroid of a lower iodine content or with lactose or sodium chloride' *U S P*.

For description and standards see the *U S Pharmacopeia* under Thyroid.

THYROXIN—'An active physiological principle obtained from the thyroid gland, or prepared synthetically, and contains when dried over sulfuric acid for 18 hours, not less than 64 per cent of iodine as an integral part of the Thyroxin molecule —' *U S P*.



For description and standards see the *U S Pharmacopeia* under Thyroxin.

Thyroid-*U S P* are indicated in cases of diminished or absent thyroid functioning, such as cretinism and myxedema. Reports show that either preparation affects the pulse rate, blood pressure, nitrogen metabolism, relieves symptoms of myxedema and will produce hyperthyroidism. The most important quantitative measure is the determination of the

basal metabolic rate. One milligram (0.001 Gm.) of thyroxin increases the basal metabolic rate 25 per cent. The relative weight in grams increases

the basal metabolic rate that the pharmacologic action of thyroxin can be followed best. When given intravenously, there is no immediate effect except occasionally when an increase in pulse rate and respiration occurs which however, will soon disappear. There may be loss of weight and nervous manifestations. If the dosage is continued for five or six days, the typical so called hyperthyroid symptoms may be produced: loss of weight, increased pulse rate with tachycardia, nervous manifestations and a sense of fatigue. With small doses the harmful effects are not produced and a stimulating effect is manifest in cases of myxedema. The amount of thyroxin required to produce toxic effects is exceedingly small. The maximum effect from a single injection is not reached until the second day, the duration of the effects being several weeks. In clinical medicine there is almost no use made of Thyroxin since Thyroid U. S. P. is simpler to use, less expensive and does not require special solution in alkali before administration.

In some forms of goiter (such as simple adolescent colloid goiter), the function of the thyroid is defective and the administration of thyroid or thyroxin may be indicated. Whereas iodine in moderate amounts is frequently helpful in causing regression in size of a colloid goiter before age 20, this is seldom observed later in life. On the other hand the use of thyroid or thyroxin has in some cases led to the diminution in size of goiter in the late second or the third decade. A few cautious trials suggest that thyroid or thyroxin may be useful in causing at least a temporary remission in the thyrotoxic process but it is not safe to depend on thyroid or thyroxin as routine medication in preparing the exophthalmic patient for surgery.

Thyroxin and thyroid have been used in obesity but increasing knowledge of this condition indicates that its treatment by restriction and management of the diet is preferable to any drug therapy.

Dosage—From 0.2 mg. to 2 mg. Thyroxin should always be given at first in minimum doses and in each case the optimum amount determined by trial. For the exact determination of this dose the establishment of the basal metabolic rate for the patient is necessary. In cases of myxedema, 0.2 mg. to 0.4 mg. should be given daily or every other day.

Thyroxin is intended for intravenous administration and is relatively ineffective by mouth. Place a known amount of pure crystalline thyroxin—from 1 to 10 mg.—in a small sterile test

tube, such as is used for the Wassermann test. Add 1 drop of 10 per cent sodium hydroxide solution and about 1 cc of water. Warm and agitate the solution until the crystals are dissolved and then sterilize by placing the tube in boiling water. Transfer the solution to a sterile hypodermic syringe, rinse out the test tube with 1 cc of sterile distilled water, adding this to the solution in the syringe, and then inject the contents of the syringe intravenously.

In many cases, after symptoms of hypothyroidism have disappeared, remarkably small doses suffice to keep the patient in an almost normal state. The patient should be careful of exertion and should take sufficient protein in the diet to compensate for increased loss of nitrogen from the action of the drug.

HOFFMANN LA ROCHE INC

Solution Synthetic Thyroxin 1 cc ampuls 1 mg per cc and 15 cc bottle 2 mg per cc

Tablets Synthetic Thyroxin 1 mg

E. R. SQUIBB & SONS

Thyroxin Crystals (For Intravenous Use) 10 mg vials

THYROXIN FRACTION—The partially purified disodium salt of thyroxin, approximately 25 per cent admixed with the acid insoluble humus like products of protein hydrolysis.

Actions and Uses—The same as those of thyroxin except that it is not to be used for injection. In certain individuals in whom the thyroxin equivalent is not absorbed quantitatively the pure crystalline thyroxin should be given intravenously (see under Thyroxin).

Dosage—Thyroxin fraction is supplied in the form of tablets for oral administration representing a stated weight of thyroxin. Thyroxin fraction must not be administered intravenously.

Tests and Standards—

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| Thyroid glands of animals | are hydrolyzed by treatment with sodium | soluble materials |
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Thyroxin fraction is a light brown powder having a characteristic odor and an alkaline taste. It is soluble in water, decomposed by acids. The following method may be applied for the assay of the tablets.

Weigh accurately five or ten tablets. Grind finely the tablets and weigh out a sample of the powdered material for analysis, place over sulfuric acid in a desiccator for twenty-four hours and determine loss in weight. Deliver the dried sample in a beaker and add 10 cc

sodium hydroxide solution, 30 per cent. Dissolve the sample by 'working' it with the aid of a glass rod; add 50 cc of water. Filter the solution into a small beaker, wash the original beaker and filter paper with sodium hydroxide test solution. Make the filtrate faintly acid with dilute sulfuric acid solution. Filter off the precipitate and wash it. Determine the iodine content in the precipitate according to the method of Kendall (*Jour. Biol. Chem.* 10:252, 1914), and calculate the amount of thyroxin in the dried specimen and in tablets. (The iodine in the precipitate is thyroxin iodine, any iodine in the filtrate is from other iodine containing compounds, and is physiologically inactive. Thyroxin fraction tablets contain a small amount of human like substance resulting from the hydrolysis of the protein.)

L. R. SQUIBB & SONS

Tablets Thyroxin Fraction: Equivalent to 0.2 mg, 0.4 mg, 0.8 mg and 20 mg. of thyroxin

Manufactured by license of the University of Minnesota U S patents 1 392 767 and 1 392 769 (Oct. 4 1921, expired)

CHAPTER XIX

METABOLIC AGENTS

Amino Acid Preparations

AMIGEN—A hydrolysate of casein prepared by digestion with porcine pancreas. Amigen is claimed to include all essential amino acids and some di- and tri-peptides.

Actions and Uses—Clinically, amigen is effective as a means of creating a positive nitrogen balance and can be used as a source of dietary nitrogen. It is not designed to cure disease but to supply nourishment. It may be administered by mouth or injected intravenously and probably is metabolized as required by the tissues.

Dosage—Amigen is available in powder form for oral use and in solution for parenteral use. The dosage is determined by the weight and physical condition of the patient, past dietary history and present food nitrogen intake. An adequate protein intake for adults is about 1 Gm. per kilogram of body weight per day. For practical purposes 1 Gm. of amigen may be regarded as approximately equivalent to 1 Gm. of protein. Nine Gm. of amigen is claimed to provide 33 calories.

Parenteral administration of amigen is indicated when the patient cannot or should not obtain sufficient protein by mouth and when the patient cannot assimilate protein. It is contraindicated in the presence of severe hepatic insufficiency and in acidosis until the latter condition is corrected. Unfavorable effects include nausea, vomiting, hyperpyrexia, vasodilatation, abdominal pain, twitching and convulsions, edema at the site of injection, phlebitis and thrombosis. Injections should be discontinued immediately if alarming reactions occur.

Solution of amigen should not be used if it is cloudy or if sediment is present. Once the bottle is opened, all the solution must be used during one injection and any part not used must be discarded. The unopened bottle should be stored in a cool place.

MEAD JOHNSON & COMPANY

Amigen Powder, 454 Gm. containers

Amigen 5% in 5% Dextrose Solution. 1 liter of 125 cc., 500 cc. and 1100 cc. Each 100 cc. contains 5 Gm. of amigen.

Amigen 10% Solution. 125 cc. and 150 cc. bottles. Each 100 cc. contains 10 Gm. of amigen.

Calcium Compounds

Calcium performs important functions, especially in forming the structure of bone, in the regulation of nervous and muscular activity, and in the coagulation of the blood. In rickets, osteomalacia and osteopsathyrosis there is defective deposition of calcium in the bones, but this is usually due to factors other than a deficient supply of calcium, and these conditions are not benefited by the administration of calcium salts except in rare experimental conditions when calcium has been almost totally lacking in the diet. When the calcium content of the blood is low, as in infantile and parathyroid tetany, the administration of calcium salts results in a temporary increase in blood calcium and a cessation of the symptoms, but unless the

The administration of calcium salts has been shown to lessen the tetanic contraction phenomena. There is some clinical evidence that calcium salts for various

edema. Intravenous fluids have been shown

to be effective in lessening peristalsis and therefore is useful in certain types of intestinal and gallbladder pain (Aub and Bauer, *J A M A* 96:1216 and *Am J Physiol* 97:1421, 1931). Calcium chloride has been shown to be useful in treating edema in certain types of Bright's disease and the ascites of cirrhosis of the liver. It is unreliable against ascites and other generalized edemas. It has been reported as being effective in preventing arsphenamine reactions and also in certain dermatoses, as dermatitis herpetiformis, lichen rubra and erythema pernio, but further observations are needed in these directions. A deficiency of calcium in the circulating fluids leads to increased excitability of the neuromuscular system, as is seen for example in tetany. The administration of calcium salts decreases the neuromuscular irritability in such cases. The intravenous infusion of soluble calcium salts causes a constriction of the blood vessels and a marked contraction of the pupils.

Calcium is necessary for blood coagulation but a large excess lengthens the coagulation time. The effect of calcium on blood coagulation has led to its injudicious use in hemorrhagic conditions such as hemophilia, purpura and the intestinal hemorrhage of typhoid fever. It is very improbable that it is effective in any of these conditions as in all of them the blood contains an adequate amount of calcium. It has been shown that the administration of calcium salts tends to diminish the toxicity of carbon tetrachloride. When calcium chloride is administered the basic portion of the molecule is, to a large extent, excreted by way of the bowel. The acid portion behaves in the same manner as hydrochloric acid from other sources, decreasing the alkali reserve of the body and increasing the acidity of the

urine. Large doses of calcium chloride may produce acidosis. Calcium chloride is one of the substances which may be administered to render the urine acid.

Intravenously, overdoses of calcium compounds may be fatal by paralyzing the heart and central nervous system.

It has been reported that not infrequently the American diet contains barely a sufficient amount of calcium to meet the needs of the organism, or may actually be deficient in this element. Furthermore,

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tration of calcium salts in the treatment of rickets or other diseases associated with deficient calcification is in itself inefficient, but may be used as an adjunct in the treatment when

from the administration of any other calcium salt. The lactate and gluconate are, however, more pleasant to take than calcium chloride and are less irritating. Calcium chloride cannot be used for subcutaneous or intramuscular injection as it is too irritating. It may, however, be used intravenously. For hypodermic or intramuscular use, the less irritant lactate or the non irritant gluconate are employed.

AFENIL — Calcium chloride urea — $\text{CaCl}_2 \cdot 4(\text{NH}_2)_2\text{CO}$ — Afenil is a molecular compound of calcium chloride and urea.

Actions and Uses—Afenil has the actions of calcium chloride. It is claimed that afenil solutions when administered intravenously, are better tolerated and less irritating than solutions of calcium chloride.

Dosage—Afenil is marketed in ampuls containing 10 cc. of a 10 per cent solution of afenil. Each injection consists of the entire contents of one ampul.

Tests and Standards—

Afenil occurs as colorless crystals, non hygroscopic, very soluble in water.

The calcium content of afenil is determined by precipitating with ammonium oxalate in the usual way and weighing as calcium oxide. The urea content of afenil is determined by an estimation of nitrogen by the Kjeldahl method.

BILHUBER KNOLL, CONS.

Solution Afenil: 10 cc. ampuls of a sterile 10 per cent solution (equivalent to 0.11 Gm. Ca).

U. S. trademark 170032. German patent 376,924.

CALCIUM GLUCONATE—‘Contains not less than 8.8 per cent and not more than 9.3 per cent of calcium (Ca) corresponding to not less than 99 per cent of $\text{Ca}(\text{C}_6\text{H}_{11}\text{O}_7)_2 \cdot \text{H}_2\text{O}$ ’
U S P

For description and standards see the U S Pharmacopeia under Calcium Gluconate and Injection Calcium Gluconate

Actions and Uses—Calcium gluconate is used to obtain the therapeutic effects of calcium. It is more palatable than calcium chloride for oral administration. Abscess formation has been reported from the intramuscular injection of the 10 per cent solution in infants.

Dosage—Orally, for adults, 5 Gm three times a day, for children, 2 Gm three times a day. Intramuscularly or intravenously, for adults, 1 Gm administered every day, on alternate days or every third day, for children, 0.2 to 0.5 Gm administered every day, on alternate days or every third day.

CALCIUM LEVULINATE—The dihydrated normal calcium salt of levulinic acid— $(\text{CH}_3\text{COCH}_2\text{CH}_2\text{COO})_2\text{Ca} \cdot 2\text{H}_2\text{O}$ —
M W 306.32

Actions and Uses—Calcium levulinate is used to obtain the therapeutic effects of calcium. It may be administered orally or intravenously and is virtually nonirritant for subcutaneous or intramuscular injection.

Dosage—By injection, for adults 1 Gm daily or on alternate days, for children 0.2 to 0.5 Gm. Orally for adults 4 to 5 Gm three times a day, for children 1 to 2 Gm three times a day.

Tests and Standards—

Calcium levulinate occurs as an odorless or nearly odorless, white, crystalline or amorphous powder possessing a bitter, saline taste. It is freely soluble in water, slightly soluble in alcohol and insoluble in acetone and ether. It melts to a syrup between 119 and 125 C with slight decomposition when the bath is heated to 100 C before introducing the specimen. The pH of the 10 per cent solution of calcium levulinate is from 7.0 to 8.5.

Dissolve 1 Gm of calcium levulinate in 10 cc of water; a clear colorless solution is formed. A 5 cc portion of this solution responds to the U S P tests for calcium. To the other 5 cc portion add 5 cc of sodium hydroxide solution; filter and add to the filtrate 5 cc of iodine test solution; the iodine color disappears and a pale yellow precipitate of iodoform appears.

Dissolve 0.1 Gm of calcium levulinate in 2 cc of water and add a saturated solution of 2,4,6-triphenylhydrazine in 2 N hydrochloric acid. Allow the mixture to stand for one hour in an ice bath; a white precipitate of calcium 2,4,6-triphenylhydrazone appears.

Dissolve 0.1 Gm of calcium levulinate in 2 cc of water and add a saturated solution of 2,4,6-triphenylhydrazine in 2 N hydrochloric acid. Allow the mixture to stand for one hour in an ice bath; a white precipitate of calcium 2,4,6-triphenylhydrazone appears.

levulinate in 10 cc of water and add 5 cc of sodium hydroxide solution; filter and add to the filtrate 5 cc of iodine test solution; the iodine color disappears and a pale yellow precipitate of iodoform appears.

Four Gm of calcium levulinate show no more *chloride* than corresponds to 1 cc of fiftieth normal hydrochloric acid (U S P XII p 626). Eight Gm of calcium levulinate show no more *sulfate* than corresponds to 1 cc of fiftieth normal sulfuric acid (U S P XII p 626). Dissolve 1 Gm of calcium levulinate in 10 cc of 5 per cent sulfuric acid add 1 cc. of bromine solution and heat for five minutes. 5 cc of the solution meets the requirements of the U S P XII test for arsenic. Dissolve 2 Gm of calcium levulinate in sufficient water to make exactly 25 cc. This solution yields no more color than a control containing 0.02 mg of lead when compared according to the U S P VII test for heavy metals.

Dry about 1 Gm of calcium levulinate accurately weighed contained in a tared weighing dish of 40-50 mm diameter in a hot air oven at 105 C for 24 hours the loss in weight is not less than 10.8 per cent nor more than 11.7 per cent.

Transfer about 30 Gm of calcium levulinate accurately weighed to a 500 cc calibrated flask using a small quantity of water, add 10 cc of hydrochloric acid and dilute to the mark with water. Transfer 100 cc of the solution to a 250 cc beaker heat to boiling and continue the assay for calcium as directed in the U S P XII under Calcium Gluconate. Each cc of tenth normal potassium permanganate is equivalent to 0.0135 Gm of anhydrous calcium levulinate the amount of calcium levulinate found corresponds to not less than 98 per cent nor more than 100.5 per cent calculated to the dried substance.

BURROUGHS WELLCOME & Co, INC

Hypoloid Calcium Levulinate Injection 10%, Solution
1 Gm in 10 cc

CHEMO PURO MANUFACTURING CORP

Calcium Levulinate 30 Gm and 480 Gm bottles

PAUL LEWIS LABORATORIES, INC

Calcium Levulinate (Powder) bulk Packed in 45.3 Gm and 2165, 453, 10825, 2165 and 453 Kg packages

CARROLL DUNHAM SMITH PHARMACEUTICAL CO

Calcium Levulinate Injection 10% W/V 1 Gm in 10 cc

Iodine Compounds for Systemic Use

These are typified by sodium iodide and potassium iodide. The mechanism of their action is not clearly understood. The most definite results are seen in the rapid absorption of certain inflammatory exudates and especially of the gummatous lesions

in very small amounts are effective in the prophylaxis of simple endemic goiter, and in controlling the symptoms of hyperthyroidism in preparation for operation.

Iodine compounds with proteins and fats have been introduced with claims that they are less irritating to the digestive tract and that they are less inclined to set up the disagreeable symptoms of iodism, such as coryza and skin eruptions. Experience confirms in a measure the former claim, but the latter is misleading. Iodism is probably a necessary manifestation of the full physiological activity of the drug. If, therefore, a preparation consistently fails to elicit these characteristic symptoms, it may be presumed that the amount of the drug absorbed is insufficient to produce the full effects, such as are required in the treatment of syphilis, although it may suffice in conditions for which a milder action is desired. Clinical observations establish the fact that the organic iodides, in the dosage ordinarily employed, are weaker than full doses of the inorganic forms.

Warning. The intravenous injection of sodium iodide is a dangerous proceeding. While it is tolerated in many cases without bad effects, it may produce not only acute and violent iodism, but also colloidoclastic shock and pulmonary edema. It should therefore not be employed to secure the ordinary actions of iodides except in very special and restricted conditions, such as (1) certain rare cases of acute thyrotoxicosis with severe vomiting, and (2) in severe paroxysms of asthma.

Sodium Iodide

SODIUM IODIDE—When dried to constant weight at 120° C, contains not less than 99 per cent NaI. *U. S. P.*

For description and standards see the *U. S. Pharmacopeia* under Sodium Iodide and the *National Formulary* under Ampuls of Sodium Iodide.

Actions, Uses and Dosage—See the general article Iodine Compounds for Systemic Use.

ENDO PRODUCTS, INC.

Sodium Iodide, 10% (W/V) 10 cc ampuls
 Each 10 cc contains 1.0 Gm of sodium iodide

LAKE SIDE LABORATORIES, INC.

Solution Sodium Iodide, 10% (W/V) 10 cc ampuls
 Each 10 cc contains 1.0 Gm of sodium iodide

SIOMINE—Hexamethylenetetramine tetraiodide—Methenamine tetraiodide $(CH_2)_6N_4I_4$. Siomine contains 78.5 per cent of iodine.

Actions and Uses—Siomine is decomposed in the intestine to the formation of hexamethylenetetramine and iodide, the rate of decomposition being essentially the same as that of hexamine. It reduces the effects of ordinary iodides in that it can be administered in much smaller doses.

Contraindications

No therapeutic claims are made for the hexamethylenetetramine component of siomine, which serves only to render the iodine insoluble. While ordinarily the hexamethylenetetramine content of siomine may be ignored, the drug should be discontinued if any signs of hexamethylenetetramine intolerance arise, such as vesical irritation or hematuria.

Dosage—The same as that of potassium iodide. Siomine is best administered in capsule form during or immediately following meals.

Tests and Standards—

Siomine is a red powder having a slight, but characteristic odor and taste. When heated to 138 C. it decomposes with violence.

Siomine is slightly soluble in acetone, alcohol, chloroform, carbon disulfide and ether (with partial decomposition). It is almost insoluble in water, but dissolves with decomposition in aqueous solutions of alkali iodides and of sodium thiosulfate and in diluted hydrochloric acid.

Heat 5 Gm. of siomine with 15 cc. of diluted sulfuric acid. First vapors of iodine (recognized by their color and effect on starch paper) are evolved; later, formaldehyde is given off (recognized by its odor and the blackening of paper moistened with silver ammonium nitrate solution). Heat the siomine-sulfuric acid mixture until it is colorless, supersaturate with potassium hydroxide solution; ammonia is evolved (recognized by its odor and effect on red litmus paper). To 0.5 Gm. of siomine add a drop of strong sulfuric acid; decomposition occurs with evolution of brown fumes.

Warm 0.5 Gm. of siomine with 0.5 cc. of water until a clear solution results; the addition of a few drops of barium chloride solution does not produce a precipitate (*sulfates*).

Incinerate a weighed quantity of siomine; not more than 0.03 per cent of ash remains.

ITMAN MOORE COMPANY

Capsules Siomine (0 mg., 0.13 Gm. and 0.3 Gm.)

U. S. patent 1,226,394 (May 15, 1917, expired). U. S. trademark.

07-99*

Iodized Fats and Fatty Acids

Iodized fats and iodized fatty acids produce in general the same systemic effects as ordinary (inorganic) iodides, but their iodine is more slowly absorbed and excreted and therefore more persistently retained, especially in tissues rich in lipoids such as the nervous structures.

The iodized fats and fatty acids generally pass the stomach unchanged and are saponified and absorbed in the small intestine, like ordinary fats. They are then deposited for the most part in lipid tissues, where they are gradually oxidized, yielding

inorganic iodide which is given off to the blood and excreted. The iodine content of the blood is thus maintained more uniform than when inorganic iodides are administered.

It is conceivable that iodized fats and fatty acids have therapeutic advantages over ordinary iodides when a gradual long sustained iodide action is desired, but the clinical evidence is not decisive. The doses used in these conditions as a rule are not irritating to the stomach and are not likely to produce iodism. Hypodermic injections remain unabsorbed for long periods and do not produce systemic actions except in very hypersensitive individuals for instance in tuberculosis.

LIPIODOL — See Lipiodol 40% Iodine under Iodized Oils

E. FOUGERA AND COMPANY, INC.

Capsules Lipiodol 40% Iodine 0.5 Gm. Each gelatin capsule contains lipiodol equivalent to 0.2 Gm. of iodine.

Dosage—Two to five capsules daily after meals.

LIPOIODINE — See Lipiodine under Iodized Oils

GIBA PHARMACEUTICAL PRODUCTS, INC.

Tablets Lipiodine* 0.3 Gm. (uncoated)

Dosage—From 0.3 to 0.6 Gm. daily or in acute cases from 1.2 to 1.8 Gm. daily. Lipiodine tablets should be masticated before swallowing.

(1) 100% Iodine

It of the iodized fatty acids of 23 to 25 per cent of iodine in

s used as a substitute for the article, Iodized Fats and Fatty

ALCIDS

Dosage—The iodine content of oridine 1 Gm. is approximately equivalent to sodium iodide 0.28 Gm. and to potassium iodide 0.31 Gm. When used for the prophylaxis of goiter 10 mg. to 30 mg. per day is given until 40 doses have been taken.

Tests and Standards—

Oridine is a light brown powder almost odorless and tasteless. It is almost insoluble in water, benzene, ether and alcohol, slightly soluble in chloroform and carbon tetrachloride.

Mix oridine 1 Gm. with water 20 cc. and filter. The filtrate becomes but slightly opalescent on the addition of silver nitrate solution (*soluble iodides*).

Mix about 0.5 Gm. of oridine accurately weighed in a nickel crucible with a mixture of powdered sodium hydroxide 4 parts and potassium nitrate 1 part and heat until fusion has been completed. Cool and dissolve the fused mass in 150 cc. of water warming to hasten solution. Filter into a 400 cc. beaker and wash well. Add 25 cc. of

tenth normal silver nitrate (the amount of silver is k in the formula below) then add slowly with stirring nitric acid until acid in reaction to litmus paper. Filter the solution through a weighed Gooch crucible, wash and titrate the excess silver nitrate in the filtrate with tenth normal potassium thiocyanate (the amount of silver in the filtrate is a). The precipitate in the Gooch crucible (consisting mainly of silver iodide with some silver chloride) is further washed with 3 portions of alcohol then either dried at 100°C and weighed (w). The amount of iodine can be calculated according to the formula

$$x = \frac{527w + a - k}{293}$$

where w equals combined weight of silver iodide and silver chloride, x equals weight of silver iodide and $(w-x)$ equals weight of silver chloride. By this method the product contains not less than 23 per cent nor more than 25 per cent of iodine. (Chlorine is used in the manufacture of iodine so that the finished product contains from 1 to 3 per cent of combined chlorine.)

F. L. LILLY AND COMPANY

Oridine (Powder): bulk

U. S. trademark 181833

Tablets Oridine: 1 equivalent to 10 mg. iodine. This dosage form is used only for prophylaxis against gastric and for the treatment of simple gastric.

RIODINE (Astier)—A 66 per cent solution in oil of an iodine addition product of castor oil. Riodine (Astier) contains about 17 per cent of iodine.

Actions and Uses—Riodine (Astier) is used as a substitute for the inorganic iodides. See preceding article, Iodized Fats and Fatty Acids.

Dosage—From 0.4 to 1.2 Gm. per day, in pearls taken after meals. Supplied only in the form of pearls.

Preparation and Tests—

Riodine (Astier) is prepared by treating castor oil with hydrogen iodide.

Riodine (Astier) is an oily liquid of light amber color, or having a faint yellow tinge, and is soluble in water and in alcohol.

When heated it is decomposed and gives evolution of hydrogen gas. When heated with a strong oxidizing agent it is oxidized to a brown color.

GALLIA LABORATORIES, INC.

Iodine Pearls: 0.2 Gm.

U. S. trademark 17744

CALCIUM IODOBIPHOSPHATE— $\text{Ca}_2(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ (molecular weight 376.12). It is a white, crystalline powder, soluble in water, forming a colorless solution. It is stable in air and is not affected by acids. It is used in the preparation of iodine supplements. It contains 23.5 per cent of iodine.

For description and standards see the U S Pharmacopeia under Calcium Iodobehenate

Actions and Uses—Calcium iodobehenate is used as a substitute for the inorganic iodides See preceding article Iodized Fats and Fatty Acids

Dosage—0.5 Gm

WINTHROP CHEMICAL COMPANY, INC

Sajodin Calcium Iodobehenate bulk

Tablets Sajodin 65 mg and 0.52 Gm

U S patent 839 509 (Dec 25 1906 expired) U S trademark 61 730

CHAPTER XX

PARENTERAL SOLUTIONS

Dextrose

DEXTROSE —*d* Glucose — $\text{CH}_2\text{OH} \overset{\text{O}}{\text{CH}} (\text{CHOH})_4 \text{CHOH}$
 H_2O 'A sugar usually obtained by the hydrolysis of starch'
U S P

For description and standards see, the U S Pharmacopeia under Dextrose Dextrose Injection and Dextrose and Sodium Chloride Injection

Dextrose is a readily absorbable food Its solutions which are being extensively used in modern therapy may be administered for parenteral use in the following amounts:

| | |
|--------------------|----|
| for parenteral use | 15 |
| injection | 5 |
| they are used | 1 |
| temporarily or | 0 |
| supply dextrose | 1 |

intestinal tract The strength of the solution the medium (distilled water, isotonic solution of sodium chloride or Ringer's solution) as well as the total quantity and route of administration must be varied to meet the indications of the individual case

Subcutaneous injections are necessarily low in dextrose content (2.5 per cent in isotonic solution of sodium chloride) intravenous solutions may vary in strength from 5 to 50 per cent of dextrose Slow rate of flow is essential to the proper administration of these solutions and is especially important in cases of hemorrhage which are not entirely controlled If it is necessary to supply very large amounts of dextrose to the individual in a relatively short time small amounts of high concentration are generally preferable to greater amounts of lower concentration

These solutions are often warmed so that they may enter the vein at body temperature The entire apparatus (bottle or flask rubber tubing connections and needle) must be sterile and the entire line of rubber tubing as well as the needle must be freed of air bubbles before the needle is inserted The area in which the needle is injected must also be adequately prepared The intake air should be filtered by a cotton pledget or other adequate device

The administration of these solutions should be instituted by a physician and continued under his supervision (especially intravenous injection) and must be discontinued before the container is empty Intraperitoneal injections are not recommended because they cause distention which may be prolonged and may induce a sterile peritonitis with polymorphonuclear exudation

Frequently apparatus used for the administration of intravenous solutions is used repeatedly. Before the apparatus is again used it must be sterilized, this sterilization process to be preceded by rinsing several times in distilled water. This should eliminate any untoward reactions which may be due to the lack of such thorough cleansing.

Since the official dextrose of the U S P XII contains one molecule of water of crystallization physicians should bear in mind that a solution labeled in terms of dextrose U S P will actually contain a less amount of anhydrous dextrose. However, in prescribing there should be reference to hydrous dextrose in conformity with U S P practice. The physician should bear in mind that in more concentrated solutions of dextrose there is considerable variation in content when comparing dextrose percentage calculated on the basis of content of the hydrous and anhydrous forms. This amounts to approximately 5 Gm in 100 cc in case of a 50 per cent solution. Manufacturers are encouraged to label their products in terms of per cent (W/V) of dextrose U S P.

Many parenteral solutions are offered in special containers bearing special trademark designations. Most of these have been examined by the A M A Chemical Laboratory and many formerly were described in New and Nonofficial Remedies. Included are containers bearing such names as Vacoliter (Baxter Laboratories Inc and Don Baxter, Inc), Safteflask (Cutter Laboratories), Filtrur (Hospital Liquids Inc).

Dosage—The dosage of dextrose in a single injection varies with the strength of the solution and may range between 5 and 250 Gm with the different purposes for which the solutions are used.

Chlorides

ISOTONIC SOLUTION OF SODIUM CHLORIDE

—Physiological Solution of Sodium Chloride—Physiological Salt Solution—Normal Saline Solution. Contains in each 100 cc not less than 0.88 Gm and not more than 0.92 Gm of NaCl. U S P.

For description and standards see U S Pharmacopeia under Isotonic Solution of Sodium Chloride.

Actions, Uses and Dosage—Isotonic solution of sodium chloride is the most commonly used saline solution and is generally employed by parenteral injection for the restoration of the body water in dehydration or for temporary replacement of the circulating blood volume. It is not the fluid of choice in the presence of acidosis. On the basis that one third of the extracellular fluid may be lost in severe anhydremia and that the extracellular fluid represents one fourth of the body weight such cases would require an amount of isotonic fluid equal to one twelfth of the body weight.

Isotonic solution of sodium chloride is also used in special containers as a diluent for the aspiration storage and administration of blood plasma obtained by centrifugation or sedimentation of citrated whole blood. For this purpose the plasma is diluted with an equal volume of the solution.

ISOTONIC SOLUTION OF THREE CHLORIDES

—Ringer's Solution— Contains in each 100 cc. not less than 0.84 Gm. and not more than 0.88 Gm. of NaCl not less than 25 mg. and not more than 35 mg. of KCl and not less than 30 mg. and not more than 36 mg. of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ U. S. P.

Certain modifications of this formula have previously been used which include the addition of 20 mg. of magnesium chloride per 100 cc. and/or 30 mg. of sodium bicarbonate per 100 cc. Ringer's solutions containing either of these ingredients are labeled accordingly.

For description and standards see the U. S. Pharmacopeia under Isotonic Solution of Three Chlorides.

Actions and Uses—Isotonic solution of three chlorides is used in all forms of dehydration but particularly in cases in which loss of gastrointestinal secretions has resulted from vomiting, diarrheas or fistulas when sodium, potassium and calcium have been diminished. It is also used in acidosis or alkalosis for improvement of circulation and stimulation of renal activity.

Dosage—Isotonic solution of three chlorides is injected by all parenteral routes according to the extent of the loss of the cations present in the solution and the extracellular body fluid.

Sodium Citrate

SODIUM CITRATE— Sodium citrate when dried to constant weight at 150°C contains not less than 99 per cent of $\text{C}_6\text{H}_5\text{OH}(\text{COONa})_3$. —U. S. P.

For description and standards see the U. S. Pharmacopeia under Sodium Citrate and Anticoagulant Solution of Sodium Citrate and the National Formulary under Solution of Sodium Citrate.

Actions, Uses and Dosage—Sodium citrate is generally employed in aqueous solution or in isotonic solution of sodium chloride as an anticoagulant for the indirect transfusion of blood. The concentration of such solutions varies from $2\frac{1}{2}$ to 4 per cent of sodium citrate and 10 cc. of this strength is ordinarily used for admixture with each 90 cc. to 100 cc. of whole blood. This provides a concentration of sodium citrate in the resultant mixture sufficient to prevent coagulation for about forty-eight hours. Solutions are available (1) in ampuls for addition to receptacles used to receive blood from the donor by the open technic and (2) in special vacuum containers or containers with a rubber bulb attachment for the development of

than 17.2 nor less than 16.5 cc of tenth normal acid is required. Transfer a 20 cc sample of sodium *r*-lactate solution to a tared platinum dish and add 3 cc of sulfuric acid. Evaporate to dryness and incinerate at 650 C for one hour; the weight of the residue is not less than 0.230 Gm nor more than 0.242 Gm.

ABBOTT LABORATORIES

Sodium *r*-Lactate One-Sixth Molar in Distilled Water
500 cc and 1000 cc bottles. A sterile solution of sodium *r*-Lactate one sixth molar (18.7% W/V) in distilled water.

BAXTER LABORATORIES, INC.

Sodium *r*-Lactate One Sixth Molar in Distilled Water
500 cc and 1000 cc Vacoliter containers.

DON BAXTER INC.

Sodium *r*-Lactate One Sixth Molar in Distilled Water
500 cc and 1000 cc Vacoliter containers.

ELI LILLY AND COMPANY

Sodium *r*-Lactate One Sixth Molar 40 cc and 100 cc ampuls. Each 10 cc contains 1.12 Gm of sodium *r*-lactate. Each 1 volume of this solution must be diluted with 5 volumes of sterile distilled water to obtain a sterile approximately 150 tonic solution equivalent in strength to sodium *r*-lactate one sixth molar.

THE UPJOHN COMPANY

Sodium *r*-Lactate (Racemic) One-Sixth Molar in Distilled Water 500 cc and 1000 cc Upjohn Infusion Bottles. Each hundred cubic centimeters contains 1.87 Gm of sodium *r*-lactate in sterile distilled water.

Lactate Ringer's solution is prepared by neutralizing lactic acid with a solution of sodium hydroxide. Certain modifications of this formula have been used which include the addition of 20 mg of magnesium chloride and/or 30 mg of sodium bicarbonate per 100 cubic centimeters. Lactate Ringer's solution containing either of these ingredients is labeled accordingly.

Actions and Uses—Lactate Ringer's solution has essentially the same use as isotonic solution of sodium chloride and more particularly isotonic solution of three chlorides. As is the case with the other salt solutions it is approximately isotonic with body fluids and may be accompanied with various percentages

of dextrose for the purpose of supplying nourishment by vein lactate Ringer's solution is designed primarily for supplying certain mineral needs of the body and for the purpose of maintaining or helping to maintain buffer balances

Dosage—Same as for isotonic solution of three chlorides (Ringer's solution)

Tests and Standards—

Lactate Ringer's solution occurs as a clear, colorless odorless solution possessing a slightly saline taste. The specific gravity is from 1.006 to 1.007 at 25 C., and the *pH* is not below 5.0 nor above 7.5. Twenty-five cc. of the solution concentrated to 10 cc. conforms to the U. S. P. XI test for heavy metals.

Transfer 1 cc. of lactate Ringer's solution drop by drop to 4 cc. of sulfuric acid contained in a test tube and keep cool by agitation in cold water. Place the test tube and contents in the steam bath for two minutes, remove the test tube and cool the contents well, add cautiously 1 cc. of a saturated aqueous guaiacol solution; a rose color develops.

Evaporate a 20 cc. portion of lactate Ringer's solution in a beaker on a steam bath until it is reduced to about 5 cc. in volume. Transfer the evaporated liquid to a suitable test tube and dilute it to 9 cc. Add 1 cc. of freshly prepared sodium cobaltic nitrite solution and mix the contents thoroughly. Treat similarly omitting the process of evaporation, in an exactly similar test tube a 4 cc. portion of a standard aqueous solution containing 20 Gm. of potassium chloride (previously dried) in 1,000 cc., the turbidity produced by the lactate Ringer's solution at the end of fifteen minutes is less than that produced by 4 cc. of the standard solution (limit of potassium).

Transfer 5 cc. of lactate Ringer's solution to a Nessler tube, add 0.5 cc. of diluted acetic acid, 40 cc. of water and 5 cc. of ammonium oxalate solution. Dilute the solution at once to 50 cc. and mix the contents thoroughly. Treat similarly portions of a standard solution formed by dissolving 0.154 Gm. of precipitated calcium carbonate (previously dried to constant weight at 200 C.) in 10 cc. of water and 3 cc. of acetic acid, diluting the solution to 250 cc.; the turbidity produced by 5 cc. of the lactate Ringer's solution at the expiration of fifteen minutes is less than that produced by 1.25 cc. and more than that produced by 1 cc. of the standard solution (limit of calcium).

Transfer 25 cc. of lactate Ringer's solution to a drying dish, evaporate to dryness on the steam bath and dry the residue to constant weight at 150 C.; the weight of residue obtained is not less than 0.227 nor more than 0.251 Gm. Evaporate a 25 cc. portion of lactate Ringer's solution to dryness, treat the residue cautiously with an excess of sulfuric acid and ignite the residue to constant weight at 750 C.; the weight of ash obtained is not less than 0.233 Gm. nor more than 0.258 Gm.

Transfer 10 cc. of lactate Ringer's solution to a 400 cc. beaker, add 50 cc. of water and 4 cc. of diluted nitric acid; dilute the solution to 200 cc., add 15 cc. of silver nitrate solution, heat the mixture to boiling and allow to cool and stand until the precipitate is granular. Filter the precipitate on a prepared Gooch crucible, wash the precipitate well with hot water, dry it to constant weight at 140-150 C.; the chloride calculated from the silver chloride weighed is not less than 0.378 Gm. nor more than 0.400 Gm. per hundred cubic centimeters of lactate Ringer's solution.

Transfer 25 cc. of a potassium dichromate solution (7.6237 Gm. of $K_2Cr_2O_7$ per liter) to a 500 cc. Erlenmeyer flask, add 25 cc. of lactate Ringer's solution and 60 cc. of an aqueous solution of sulfuric acid (40% H_2SO_4). Place the flask and contents in a water bath at 70 C., stopper the flask when the solution attains the temperature of water bath and keep the flask and contents in the water bath for one hour. Cool the solution, add 200 cc. of water and 8 cc. of potassium iodide solution (10% KI), stopper the flask and mix the contents well; allow

the solution to stand for ten minutes in a dark place and titrate the liberated iodine with tenth normal sodium thiosulfate using starch test solution as indicator. Make a blank test at the same time with the same quantities of reagents and correct the assay accordingly. Each cubic centimeter of dichromate solution corresponds to 0.003501 Gm of $\text{CH}_3\text{CHOHCOOH}$. The amount of dichromate solution consumed corresponds to not less than 0.233 Gm nor more than 0.265 Gm of lactic acid ($\text{CH}_3\text{CHOHCOOH}$) and to not less than 0.290 Gm nor more than 0.330 Gm of sodium lactate ($\text{CH}_3\text{CHOHCOONa}$) per hundred cubic centimeters of lactate Ringer's solution.

ABBOTT LABORATORIES

Lactate Ringer's Solution 500 cc and 1000 cc bottles
Each hundred cubic centimeters contains sodium lactate 0.31 Gm sodium chloride 0.6 Gm potassium chloride 30 mg and calcium chloride 20 mg

BAXTER LABORATORIES INC

Lactate Ringer's Solution 500 cc and 1000 cc Vacoliter containers

DON BAXTER INC

Lactate Ringer's Solution 500 cc and 1000 cc Vacoliter containers

CONTINENTAL HOSPITAL SERVICE INC

Lactate Ringer's Solution 500 cc and 1000 cc bottles

ELI LILLY AND COMPANY

Ampoules Lactate Ringer's Solution 25 Times Concentrated 10 cc and 20 cc. When 1 volume of the solution is diluted with 24 volumes of sterile distilled water. The diluted solution is equivalent in strength to lactate Ringer's solution N N R

THE UPJOHN COMPANY

Lactate Ringer's Solution 500 cc and 1000 cc Upjohn Infusion Bottles. Each hundred cubic centimeters contains sodium lactate 0.31 Gm sodium chloride 0.6 Gm potassium chloride 40 mg and calcium chloride 20 mg in redistilled water

CHAPTER XXI

PHARMACEUTIC AND THERAPEUTIC AIDS

CHLORINATED PARAFFIN — Chlorocosane — 'A liquid paraffin which has been treated with chlorine' *N F*

For description and standards see the National Formulary under Chlorinated Paraffin

Actions and Uses — The chlorine of chlorinated paraffin is therapeutically without action. Chlorinated paraffin is used as a solvent for dichloramine T. With it solutions containing up to 8 per cent may be prepared. The high viscosity of the oil prevents its being readily sprayed with a hand spray, the addition of about 10 per cent carbon tetrachloride will reduce the viscosity so that it can be readily sprayed in an ordinary oil atomizer.

GELATIN COMPOUND PHENOLIZED — A mixture composed of gelatin 14 per cent, carbolic acid (phenol) 15 per cent, zinc oxide 55 per cent and glycerin 39 per cent.

Actions and Uses — Gelatin compound phenolized is used in the preparation of bandages to cover chronic ulcers and unhealed secondary burns and in the preparation of pressure bandages for varicose veins when surgical treatment is not necessary.

Dosage — For use the preparation is heated until it becomes liquid and is applied with a brush, over this a spiral bandage is applied and another layer of the preparation brushed on this is repeated until a total thickness of three layers of the bandage and four of the preparation has been applied.

SHARP & DOHME, INC

Gelatin Compound Phenolized bulk

PARRESINE — A mixture composed of paraffin (melting point 48 to 49 C), from 94 to 96 per cent, gum elemi from 0.20 to 0.25 per cent, Japan wax from 0.40 to 0.50 per cent, asphalt, from 0.20 to 0.25 per cent and eucalyptol 2 per cent. To this mixture is added from 0.5 to 1.0 per cent solution of alkanin in eucalyptol and a minute quantity of gentian violet these being employed to bring the product to a standard color. Marketed only in the form of Parresined Lace Mesh Surgical Dressing.

Actions Uses and Dosage — Non absorbent protective used for the preparation of Parresined Lace Mesh Surgical Dressing.

ABBOTT LABORATORIES

Parresined Lace-Mesh Surgical Dressing. Net mesh gauze impregnated with, and containing, from 45 to 50 per cent of parresine

U S trademark 117 636

PROPYLENE GLYCOL. — Racemic propylene glycol — Racemic 1,2-dihydroxypropane — $\text{CH}_3\text{CHOHCH}_2\text{OH}$

Actions and Uses. — Propylene glycol is used for pharmaceutical purposes as a diluent. Its toxicity is similar to that of glycerin. As ordinarily employed, it may be called practically nontoxic.

Tests and Standards. —

Propylene glycol occurs as a viscous colorless, almost odorless liquid, completely miscible with water, alcohol, chloroform and ether. The specific gravity at 25 C ranges between 1.035 and 1.037. The refractive index at 25 C ranges between 1.4312 and 1.4317.

Transfer 25 cc of propylene glycol to a distilling flask, determine the distillation range according to Method I of U S Pharmacopeia. X. Ninety-five per cent distills at from 134 to 139 C (corrected) at 769 mm. The refractive index of the distillate is the same as that of the material before distillation. Agitate 5 cc of propylene glycol with 15 cc of distilled water, insert a piece of red and a piece of blue litmus paper, the solution must be neutral to the litmus papers. Add 1 cc of silver nitrate solution and 1 cc of nitric acid to 5 cc of propylene glycol diluted with 15 cc of water, not more than slight opalescence appears within fifteen minutes (*chloride*). Add 1 cc of barium chloride and 1 cc of diluted hydrochloric acid to 5 cc of propylene glycol diluted with 15 cc of water, no precipitate forms in fifteen minutes (*sulfate*). Bubble hydrogen sulfide through 5 cc of propylene glycol diluted with 15 cc of water, there is no opalescence and no change of color.

Mix 5 cc of propylene glycol with 10 cc of distilled water in a test tube, add 1 cc of 1 per cent potassium permanganate solution, the color of the solution within 15 min.

Dissolve 10 cc of propylene glycol accurately measured in 50 cc of distilled water. Add 1 cc of phenolphthalein test solution and titrate with tenth normal sodium hydroxide until the solution remains faintly pink after shaking for 30 seconds, not more than 0.2 cc is required (*limit of acids*).

Incinerate about 2 Gm of propylene glycol accurately weighed in a platinum dish, the residue is not more than 0.05 per cent.

THIOUREA — $\text{S C}(\text{NH}_2)_2$

Uses. — Thiourea may be added to solutions of certain substances, e g, metycaïne with epinephrine, in order to prevent oxidation.

Tests and Standards. —

Thiourea is a white crystalline almost odorless solid, slightly soluble in cold alcohol, very slightly soluble in chloroform, and ether. When 0.05 Gm is dissolved in 10 cc of water to which 2 drops of ferric chloride solution have been added, the color is only slightly augmented (*sulfocyanates*). Warm 0.05 Gm of thiourea in a

test tube until it melts cool add 10 cc. of water and 2 drops of ferric chloride solution a blood red color results. Add 10 cc. of water and 4 cc of diluted nitric acid to a mixture of 0.1 Gm bismuth nitrate and 0.3 Gm of thiourea, and warm an orange colored solution results which upon evaporation yields crystals of an orange color. The melting point of thiourea ranges from 176 to 180 C.

TRIETHANOLAMINE-TECHNICAL.—A mixture containing not less than 80 per cent triethanolamine (C_3H_7OH)₃N not more than 15 per cent diethanolamine (C_2H_5OH)₂NH and not more than 25 per cent monoethanolamine C_2H_5OH NH₂.

Actions and Uses—Triethanolamine technical is an excellent emulsifying agent for use in the preparation of ointments and other dermatologic medicaments. When added to certain preparations used on the scalp for example, oil of cade it facilitates their subsequent removal. Triethanolamine technical combines with fatty acids to form soaps with good detergent properties which are soluble not only in water but also in vasoline kerosene, and oils. It is claimed to have the power of increasing the penetration of oily substances and to possess a certain amount of bacteriostatic action. Rarely an individual will be encountered who is sensitive to this compound.

Dosage—In the preparation of stable emulsions of fatty or vegetable oils the triethanolamine and oleic acid are first added to about one third of the oil. Using mechanical agitation about one third of the water is added and stirred until a thick smooth emulsion is formed. Then with continued mechanical agitation alternate thirds of oil and water are slowly stirred in. Emulsions may be made containing from 20-40 per cent of oil which may be diluted with as much as five times the volume of water. For emulsions containing olive oil, the proportions based on the weight of the oil are 2.4 per cent by weight triethanolamine and 11.5 per cent oleic acid. Substantially the same proportions are used for the majority of vegetable oil emulsions. For white paraffin oil emulsions the amount of triethanolamine should be increased to 5 per cent by weight.

Tests and Standards—

Triethanolamine technical is a colorless to pale yellow viscous hygroscopic liquid with a slight ammoniacal odor. It is miscible with water and alcohol and is soluble in chloroform, immiscible with ether, benzene and purified petroleum benzene. The specific gravity is from 1.124 to 1.130 at 25°C. The refractive index is from 1.480 to 1.485 at 20°C.

To 1 cc of triethanolamine technical add 0.1 cc of copper sulfate solution a deep blue color forms. Add 5 cc sodium hydroxide solution and concentrate to $\frac{1}{3}$ volume by boiling the color remains. To a test tube place 1 cc of triethanolamine technical add 0.3 cc of cobalt chloride solution of a slotted cork suspend a the air space slot the side of the tube in the steam-bath the paper turns blue. To 4 cc of 10 per cent aqueous solution of triethanolamine technical add 2 drops of phenolphthalein indicator solution an alkaline reaction is indicated.

Weigh and transfer 50 cc of triethanolamine technical to a suitable Ladenburg distilling flask, attach the flask to a suitable condenser with receiver and slowly and carefully fractionate at a pressure of 10 mm of mercury, not more than 8 per cent by weight of distillate is obtained below 89 C., of which 1 Gm consumes not more than 15.4 cc, nor less than 14.3 cc of normal hydrochloric acid when titrated as indicated for triethanolamine technical, not more than 5 per cent by weight of residue is left after distillation below 209 C.

Transfer 2 to 3 Gm of tri-ethanolamine technical, accurately weighed to an Erlenmeyer flask. Add 75 cc. of water and 0.1 cc of methyl red indicator solution, and titrate with normal hydrochloric acid not less than 6.7 cc, nor more than 7.8 cc of normal hydrochloric acid is consumed per gram.

The weight of the ash obtained from 1 Gm of triethanolamine technical, accurately weighed, is not more than 0.0001 Gm.

Transfer about 15 Gm, accurately weighed, of triethanolamine technical to a 100 cc beaker, add 50 cc of solution A (dehydrated alcohol saturated with triethanolamine hydrochloride) and agitate the contents until the sample is dissolved. Add 10 cc of solution B (100 cc of solution A treated with dry hydrogen chloride until the weight increases 20 Gm). Stir the contents well and set the mixture aside 5 minutes. Filter the solution through a prepared Gooch crucible and complete transfer of the precipitate by washing with 5 to 10 one cc portions of solution A. Then cover the precipitate by adding slowly 40 cc of solution A at the same time applying gentle suction to the crucible. Follow by washing with five 10 cc. portions of solution C (a mixture of 6 volumes of anhydrous ethyl ether and 4 volumes of dehydrated alcohol saturated with triethanolamine hydrochloride). Finally remove all liquid by suction, allow air to be drawn through the crucible for several minutes and dry to constant weight at 105 C. The weight of triethanolamine calculated from the weight of triethanolamine hydrochloride precipitate obtained is not less than 80 per cent of the weight of sample.

CHAPTER XXII

SEDATIVES AND HYPNOTICS

Compounds Containing Bromine

Synthetic compounds containing bromine have been produced with the purpose of securing the sedative action of bromide ion without the objectionable effects of the alkali bromides. These compounds split off bromine ions in the system, the decomposition being due to the oxidation of the organic substance with which it is combined, but bromine which is too firmly bound may fail to exert its typical effects. As the usual indications for bromide action in the organism require a prompt and powerful action on the cells to produce sleep, to abolish reflexes or to arrest an epileptic paroxysm the synthetic compounds are likely to fail as substitutes for the alkali bromides because their bromide ion is liberated too slowly. The introduction of bromine into compounds already possessing hypnotic or sedative powers may result in increasing the efficiency of these compounds.

BROMURAL — $(C_6H_5CH(C_6H_5)CHBrCO)HNCO NH_2$ — 2 monobromoisovalerylurea, obtained by the interaction of urea with bromoisovaleryl bromide

Actions and Uses—Bromural is a sedative which produces sleep in mild cases of insomnia without markedly affecting the circulation or respiration. All action by bromural is said to cease after from three to five hours. In many cases however, the sleep caused by the preparation continues beyond the limits of its action. It is useful as a sedative and for the purpose of inducing sleep in functional nervous disease. Bromural is not effective in cases of insomnia associated with pain, cough, angina pectoris or delirium.

Dosage—As a sedative 0.3 Gm., three times daily, as a hypnotic at bedtime, 0.6 Gm., which dose may be repeated if advisable during the night after three to four hours.

Tests and Standards—

Bromural forms small white almost tasteless needles which are easily soluble in hot water, ether, alcohol and alkalis, but less readily in cold water. It sublimes on heating and melts at from 147 to 149 C.

Bromural can be precipitated from a 10 per cent sodium hydroxide solution with acids. The presence of bromine may be demonstrated by fusion with sodium carbonate and potassium nitrate and testing for a bromide with silver nitrate solution. On heating the alcoholic solution of bromural with sodium ethylate for several hours on the water bath sodium bromide will precipitate. If this is filtered off and the filtrate evaporated a crystalline mass remains which can be recrystallized from water. This is dimethylacrylic acid melting at 280 C. If 1 Gm. of bromural is boiled for about one minute with 10 per cent solution of sodium hydroxide ammonia obtained from the urea will be given off. If the hot liquid is then cooled acidified with

nitric acid and extracted with ether and the ether evaporated, an oily fluid bromoisovaleric acid which has the specific odor of valeric acid will remain. The bitter reaction cannot be obtained. On melting bromural and a strong concentrated sodium hydroxide solution and copper sulfate, no color reaction will take place.

BUTHERBROOK COMPANY

Tablets Bromural 0.3 Gm

U. S. patent 914,418 (March 9, 1929, expired) U. S. trademark 61,165

CARBROMAL—From ethylacetylurea.—For description and standards see the National Formulary under Carbaronal.

Actions and Uses—Carbromal is said to be an efficient and prompt sedative reducing excitement and promoting sleep in conditions in which a powerful hypnotic is not required. In therapeutic doses it is said not to exert any unfavorable influence on the respiration or heart action. The sleep produced is said to be restful, dreamless and exceptionally free from unpleasantly effects and sequelae.

Carbromal is stated to be useful as a sedative and mild hypnotic in neurasthenia, cardiac neuroses with tachycardia, chorea, mental disorders with moderate excitement, insomnia due to various internal diseases.

Dosage—As a sedative from 0.3 to 0.6 Gm., given in cold water, repeated three or four times daily, if necessary, as a hypnotic from 0.6 to 1.3 Gm. followed by a drink of hot sweetened water or weak tea.

MILNER & Co., INC.

Carbromal Powder

THE UPJOHN COMPANY

Tablets Carbromal 0.3 Gm

WINTHROP CHEMICAL COMPANY, INC.

Adalin (Powder) bulk

Tablets Adalin 0.3 Gm

U. S. patent 993,425 (Feb. 7, 1911, expired) U. S. trademark 81,136

WYETH INCORPORATED

Tablets Carbromal 0.3 Gm

Chloral Derivatives

Chloral hydrate is still the standard hypnotic of its class but it has the disadvantages of causing cardiac and respiratory depression in overdosage and of irritating the stomach unless

diluted suitably, furthermore, it cannot be used hypodermically. Attempts to modify the drug so as to make it safer have at the same time resulted in weakening its hypnotic action. Attempts to remove its irritant action have been more successful. The chloral derivatives described below are less irritating to the stomach. Chlorobutanol can be given by hypodermic injection.

BUTYLCHLORAL HYDRATE — Butylchloral Hydrate
 $\text{C}_4\text{H}_9\text{CHCl}_2$ — Croton Chloral Hydrate
 $\text{C}_6\text{H}_5\text{CHCl}_2$ — A
 addition of water to liquid
 CH_3CHCl_2 , CHO

Actions and Uses—The action of this preparation is similar to that of chloral hydrate.

Dosage—From 0.3 to 1.3 Gm.

Tests and Standards—

Butylchloral hydrate occurs in pearly white trimetric laminae having a pungent but not acrid odor and an acrid, nauseous taste. It fuses at about 78° C. to a transparent liquid which in cooling begins to solidify at about 71° C. It is soluble in about 50 parts of water and in its own weight of glycerin or of alcohol (90 per cent); it slowly dissolves in 20 parts of chloroform. From a solution in alcohol it is precipitated by the gradual addition of water in the form of globules said to consist of butylchloral alcoholate $\text{C}_4\text{H}_9\text{Cl}_2\text{O}$. The alcoholic solution is neutral and the aqueous solution is neutral or but slightly acid to litmus.

It gives no precipitate with solution of silver nitrate. Heat about 0.2 Gm. of butylchloral hydrate with 10 cc. of sodium hydroxide solution and add 2 drops of a saturated aqueous solution of aniline; the odor of phenyl isocyanide is not evolved (chloral hydrate).

CHLOROBUTANOL — Chlorbutol — Acetone Chloroform
 — Chlorobutanol may be anhydrous or it may contain up to about one half molecule of water. *U. S. P.*

For description and standards see the *U. S. Pharmacopoeia* under Chlorobutanol.

Actions and Uses—Chlorobutanol is said to be absorbed unchanged from the alimentary tract but to be decomposed in the body. It is a local anesthetic with an action weaker than that of cocaine, but sufficient frequently to prevent vomiting from slight gastric irritation. Its antiseptic action is said to be fifteen times as strong as that of boric acid. It acts on the central nervous system similarly to chloral hydrate, and although the claim has been made that hypnotic doses are without effect on the circulation and respiration, independent observers have described a fall of blood pressure and interference with respiration in animals and consider it fully as dangerous as chloral hydrate. In man 6.5 Gm. (100 grains) caused severe symptoms but recovery occurred. It is said to be useful as a mild local anesthetic in dentistry etc. as a preservative for hypodermic

solutions and for insomnia, vomiting and spasmodic conditions. It is also said to be useful as an introductory to general anesthesia, as it lessens excitement and nausea.

Dosage—From 0.3 to 1.3 Gm, dry or in capsules. Hypodermically as a local anesthetic a saturated aqueous solution may be used.

MERCK & Co, INC

Chlorobutanol (Hydrous) bulk This product is used in the preparation of aqueous solutions.

Chlorobutanol (Anhydrous): bulk This product is used in the preparation of oil solutions.

PARKE, DAVIS & COMPANY

Chloretone: bulk

Boro-Chloretone A dusting powder composed of chloretone, 1 part, boric acid 1 part, purified talc, 2 parts.

Capsules Chloretone: 0.2 Gm and 0.3 Gm

Chloretone Inhalant Chloretone 1 Gm camphor, 25 Gm; menthol, 18 Gm oil of cinnamon 60 mg refined liquid petrolatum, 94.64 Gm

Opium Principles and Derivatives

Morphine is a complex derivative of phenanthrene. It contains two OH groups (one phenolic, the other alcoholic) in which substitutions can be made by either alkyl or acid radicals.

The more important alkyl esters are the monomethyl (codeine), the dimethyl (thebaine), and ethyl morphine. Heroin is the diacetyl derivative.

The nature of these radicals—whether acid or alcoholic, aromatic or aliphatic—modifies the actions, quantitatively, but only in degree. Replacement of one hydroxyl group (codeine) diminishes the narcotic action and increases the respiratory and tetanic action. When both OH groups are replaced by acids (diacetyl morphine) the narcotic effects are stronger than with codeine, and the tetanic action is weaker than with morphine.

Actions and Uses—The central actions of all these morphine derivatives are qualitatively identical, but they present quantitative differences which have some practical importance.

Morphine produces the strongest narcotic analgesic, hypnotic and intestinal effects, and the weakest stimulation. It causes the greatest derangement of digestion. It and diacetyl morphine are most liable to induce a habit.

Codeine (methyl morphine) is less narcotic, less constipating and less apt to induce tolerance and habit. It is, therefore especially valuable in cough or in other conditions in which the sedative action must be continued for some time and in patients who do not tolerate morphine.

Ethyl-Morphine seems to stand intermediate between morphine and codeine, in all respects. The hydrochloride is used as a sedative, but mainly for its special action on the conjunctiva.

Diacetyl-Morphine (heroin) closely approaches morphine of which it shares all the disadvantages and over which it has no important advantage. It was originally introduced with the claim that therapeutic doses lessen the cough reflex and slow the respiration, but that the inspirations are deepened and more powerful, so that the alveolar air is more effectively ventilated. Independent workers, however, have shown that there is no real difference from morphine in these respects. It is now generally conceded that diacetyl morphine is as effective as morphine in cough but not more so, that it is rather less effective against dyspnea and that it is more liable to produce habit and toxic effects.

DIHYDROMORPHINONE HYDROCHLORIDE — $C_{17}H_{19}O_3N \cdot HCl$ — U S P — Dilaudid Hydrochloride — Dihydromorphinone hydrochloride differs essentially from morphine hydrochloride in that one of the hydroxyl groups of the latter has been replaced by a ketone group and the adjacent double bond has been removed by hydrogenation.

For description and standards see the U S Pharmacopeia under Dihydromorphinone Hydrochloride and Dihydromorphinone Hydrochloride Tablets.

Actions and Uses — The base dihydromorphinone is closely allied both chemically and pharmacologically to morphine having the analgesic property of morphine as well as its action on the respiratory system. Its action on the intestine is probably less marked than is that of morphine. It is more toxic than morphine and is clinically effective in doses which are considerably smaller than are necessary with that alkaloid. It has been shown experimentally and clinically that dihydromorphinone is powerfully analgesic and that like morphine it can depress the respiratory mechanism profoundly. At the same time the experimentally established ratio between effective doses of morphine and dihydromorphinone for the production of desirable effects is not materially different from the ratio between their toxic doses. Clinical trial has not shown that dihydromorphinone is free from tolerance and addiction evoking properties and while side actions such as nausea vomiting and constipa-

tion seen to occur less frequently than with morphine the prolonged administration of dihydromorphinone should be undertaken with as much caution as would be exercised with morphine itself. Dihydromorphinone hydrochloride comes within the scope of the federal narcotic regulations.

Dosage—As a sedative and for the relief of pain the usual oral dose is 25 mg. in milliam or cough 13 mg. may be given orally. The customary hypodermic dose is 2 mg. Clinically the dose necessary to produce analgesia is about one fifth that of morphine.

BRIEFER KNOWN COM

Solution Dilaudid Hydrochloride 11 cc ampuls. Each cubic centimeter contains dihydromorphinone hydrochloride 2 mg. in isotonic solution of sodium chloride.

Dilaudid Hydrochloride Compounding Tablets 16 mg. These tablets each many times the average dose are for use in compounding only.

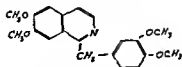
Hypodermic Tablets Dilaudid Hydrochloride 1 mg, 2 mg, 32 mg and 4 mg.

Tablet Dilaudid Hydrochloride 25 mg.

Dilaudid Hydrochloride Rectal Suppositories 25 mg. dihydromorphinone hydrochloride in cacao butter base.

German patent 380 919 (1913) U. S. trademark 298 197.

PAPAVERINE—Papaverina— $C_{20}H_{21}O_4N$ —An alkaloid obtained from opium belonging to the benzyl isoquinoline group (that is it is not a morphine derivative).



Actions and Uses—Pal found that papaverine relaxes smooth muscle in general although different organs are affected in a varying degree.

Papaverine is most effective in hypertonic conditions while it does not interfere materially with the normal movements for instance of the intestines. It is also a rather feeble central analgesic and a local anesthetic. Its toxicity is low and neither tolerance nor habituation has been reported. These actions have prompted its use with reported success in various spasmodic conditions of the smooth muscles. Pal recommends

it especially in all kinds of gastric and intestinal spasms (also for the diagnosis of pyloric spasm), in biliary colic, and in bronchial spasm. Of more doubtful value is its employment in pertussis, hyperemesis, and vascular spasm—angina pectoris, acute uremia and eclampsia. It is ineffective in chronic hypertension. The local anesthetic action, with vasodilatation, has been used against rhino asthma, to treat bronchial asthma, and to mitigate the pain of irritant injections.

Dosage—The oral and hypodermic single dose is from 30 mg to 80 mg, daily dose to 0.5 Gm. Single doses of even 1 Gm are said to be nontoxic.

Tests and Standards—

Papaverine occurs in fine white rhombic prisms or needles or sometimes in scales. It is odorless and tasteless. It is nearly insoluble in cold water; slightly soluble in alcohol, ether, chloroform and benzene if cold, somewhat more soluble in these liquids when hot, but deposited by them on cooling, and soluble in warm petroleum ether and in acetone. It melts at 147° C.

If about 0.01 Gm. of papaverine is dissolved in 10 cc. of water containing a few drops of diluted hydrochloric acid and a few drops of potassium ferricyanide solution is added, a lemon yellow precipitate of papaverine ferricyanide should form at once (*distinction from other opium alkaloids*). If about 0.001 Gm. of papaverine is dissolved in 0.1 cc. of sulfuric acid containing in each cubic centimeter 1 drop of formaldehyde solution a colorless or at most a faintly yellowish green solution should be produced. This gradually changes to deep rose and finally becomes brown (*distinction from morphine and its esters which give purple or violet colors*). If 0.01 Gm. of papaverine is dissolved in 0.2 cc. of sulfuric acid the solution should not be colored more deeply than a very faint pink or brown (*limit of cryptopine thebaine or of other organic impurities*). If 0.01 Gm. of papaverine is dissolved in 10 cc. of water containing a few drops of hydrochloric acid, a few drops of a saturated aqueous solution of indole acid added, and the mixture shaken with chloroform, the chloroform layer should not be colored violet (*morphine*).

If from 0.2 to 0.3 Gm. of papaverine is weighed, dissolved in 20 cc. of warm water containing a few drops of diluted hydrochloric acid, the solution cooled, 1 cc. of freshly prepared potassium ferricyanide solution added, the mixture agitated, allowed to stand overnight and filtered, the filtrate made alkaline with ammonia water, shaken with several successive portions of ether, the ether solutions combined, washed with water, evaporated, the residue dried at 100° C. and weighed, the weight should not amount to more than 2 per cent of the weight taken (*limit of foreign opium alkaloids*).

PAPAVERINE HYDROCHLORIDE—"The hydrochloride of an alkaloid obtained from opium" N. F.

For description and standards see the National Formulary under Papaverine Hydrochloride.

Actions, Uses and Dosage—See preceding article, Papaverine.

Sulfonmethanes

Two analogous compounds formed by the substitution of sulfone radicals in methane have been applied in therapeutics. The first sulfonmethane-N. F. (sulfonal) is diethylsulfon

dimethylmethane, the second sulfonethylmethane N F (trional) is diethylsulfonmethylethylmethane. The latter has been generally given the preference.

Sulfonmethane is soluble with difficulty and slowly absorbed and its hypnotic action is but slowly established, sulfonethylmethane is somewhat more soluble than sulfonal and acts more quickly. Both drugs are preferably given in hot liquids, and in the case of sulfonmethane the hypnotic effect is likely to be postponed for several hours. Sometimes it is not developed until the following day. Sulfonethylmethane is usually effective in an hour or two.

The sulfonmethanes in therapeutic doses produce sleep without noticeable effect on the circulation or respiration. In larger doses, acute poisoning occurs, evidenced by disturbances of the digestive organs, the metabolism and the nervous system. When administered for too long a period, emulsion is likely to occur, producing a condition of chronic poisoning which terminates fatally in a large percentage of cases. In such cases hematoporphyrin derived from hemoglobin turns the urine pink or red. This should serve as a warning, indicating the immediate withdrawal of the drug.

The symptoms of poisoning consist of persisting confusion, ataxia, constipation, vomiting, albuminuria and nephritis.

Dosage—The usual dose of either sulfonmethane or sulfonethylmethane is 10 Gm with a maximum of 2 Gm for the first and 4 Gm for the second. When these drugs are used frequently, the administration should be suspended once in two or three days to allow of complete elimination, and the urine should be examined frequently for hematoporphyrin.

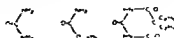
SULFONMETHANE.—Sulfonal — For description and standards see the National Formulary under Sulfonmethane.

Actions, Uses and Dosage — See preceding article Sulfonmethanes.

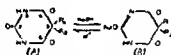
SULFONETHYLMETHANE — Diethylsulfonmethylethylmethane — For description and standards see the National Formulary under Sulfonethylmethane.

Barbituric Acid Derivatives

Barbital (diethylbarbituric acid), which was introduced under the name of "veronal," is chemically related to urea and the carbamate hypnotics.



The ethyl groups may be replaced by other alkyl or aryl radicals to form a large number of derivatives of the general structure indicated in "A"



The following compounds of their salts are described in N N R

| COMPOUNDS | R ₁ | SUBSTITUENTS | Other Substituent |
|---------------|-------------------|---------------|-------------------|
| Barbital | Fthyl | Fthyl | |
| Amytal | Ethyl | Isomyl | |
| Ipral | Fthyl | Isopropyl | |
| Neonal | Fthyl | n Butyl | |
| Ortal | Fthyl | n Hexyl | |
| Pentothal | Ethyl | 1 Methylbutyl | 2 Thio |
| Pentobarbital | Ethyl | 1 Methylbutyl | |
| Phenobarbital | Ethyl | Phenyl | |
| Phanodorn | Ethyl | Cyclohexenyl | |
| Evipal | Methyl | Cyclohexenyl | 1 Methyl |
| Alurate | Allyl | Isopropyl | |
| Dial | Allyl | Allyl | |
| Seconal | Allyl | 1 Methylbutyl | |
| Sandoptal | Allyl | Isobutyl | |
| Nostal | β Bromallyl | Isopropyl | |
| Pernoston | β Bromallyl | Butyl | |

The compounds ("acids") listed are only sparingly soluble in water, but freely soluble compounds of the general structure indicated in "B" are formed in the presence of sodium hydroxide e g, barbital sodium, U S P

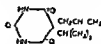
Actions and Uses—Barbital and its derivatives are effective sedatives and hypnotics and are used as such in simple insomnia, hysteria, neurasthenia, thyroid disease and chorea, in epilepsy in the intervals between the seizures, in mental disturbances and in impending delirium tremens. They also augment the action of analgesics such as aminopyrine, acetophenetidin and acetylsalicylic acid, and they are used in combination with these analgetics for the relief of pain, especially of neuralgic character. The therapeutic effects are exerted on the higher centers of the brain, and therapeutic doses do not usually cause any apparent injury to the heart circulation, or kidneys.

They are decidedly more actively hypnotic, and somewhat more analgetic than chloral hydrate, they do not produce local irritation and the taste is not disagreeable. The margin between the ordinary therapeutic dose and the toxic dose is somewhat wider than that with chloral hydrate, and small therapeutic doses have little effect on the blood pressure and

respiration. Several of the derivatives of barbitol are more actively hypnotic than the parent substance and may be preferred especially as a sedative, but there is no satisfactory evidence that the margin between the therapeutic and toxic doses of these derivatives is significantly wider than in the case of barbitol itself. The action is somewhat slower than with chloral hydrate but more rapid than with sulfonmethane. In the absence of pain small doses usually induce sleep within half an hour. The sleep lasts for four to eight hours varying with individuals with the drug used and with the dose. The patient generally awakens refreshed but occasionally there are lassitude vertigo headache nausea and diarrhea on the following day even after moderate doses. In some patients barbitol and its derivatives produce restlessness and excitement and these agents should not be used for such patients. Skin eruptions are sometimes observed. Fatal collapse (by peripheral paralysis of the blood vessels) has occurred after relatively small doses. Toxic doses cause lowered body temperature, depression of the respiration and circulation and feeble heart beat. There is long continued stupor sometimes interrupted by excitement. The condition has been confused with uremia epidemic encephalitis and opium poisoning. The slower the excretion of the various members of this group the more lasting is the action and with very slow excretion ordinary doses may produce cumulative toxic effects after some time. Death results from paralysis of respiration. It is therefore safer to intermit the administration at least weekly. Continued use may lead to addiction. Barbitol preparations are usually administered orally or rectally. Barbitol and the acid derivatives are slightly soluble in water the readily soluble sodium salts have closely similar actions after they enter the circulation.

In emergencies when prompt action is imperative, when oral or rectal administration is not feasible and in other carefully selected instances one of the soluble preparations may be injected intravenously. Certain of the briefly acting soluble barbiturates are injected intravenously as general anesthetics in selected cases but the method is not devoid of danger. It should be employed only by competent experienced anesthetists and others who are familiar with the rigid technic and who have at hand facilities for combating accidents involving respiratory depression and carbon dioxide oxygen balance. These compounds may also be used to induce anesthesia prior to its continuance by other means such as gaseous anesthetics but such technic is by no means suitable as a routine measure it should be used only in special instances such as when the patient is exceedingly apprehensive. Experimental work indicates that fairly large doses are useful against the convulsions arising from poisoning by the local anesthetics but they are harmful when the more common paralysis has resulted.

ALURATE—5 Allyl 5 isopropylbarbituric acid — Allyliso propyl-malonylurea — $C_{16}H_{24}O_4N_2$ —M W 210.23



Actions and Uses—The actions and uses of alurate are essentially similar to those of barbital, but alurate is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic.

Dosage—For mild cases of insomnia, 65 mg may be administered at bedtime. In obstinate cases 0.13 Gm may be given.

Tests and Standards—

Alurate occurs as a fine white odorless crystalline powder, with a slightly bitter taste, completely soluble in alcohol, chloroform and ether, very slightly soluble in cold water, insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Alurate melts at 140 to 141.5°C.

Place about 0.3 Gm of alurate in a glass stoppered cylinder, add a mixture of 1 cc of normal sodium hydroxide solution and 5 cc of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc of mercuric chloride solution, a white precipitate results, soluble in an excess of ammonia water; to the other portion add 5 cc of silver nitrate solution, a white precipitate results, soluble in an excess of ammonia water. Boil about 0.5 Gm of alurate with 5 cc of a 25 per cent sodium hydroxide solution, it is decomposed with the evolution of ammonia. Dissolve about 0.1 Gm of alurate in 1 cc of sulfuric acid, not more than a slight yellow color results. Place about 1 Gm of alurate in a 25 cc glass stoppered cylinder, add 10 cc of water, shake the mixture for one minute, filter through paper and divide into two portions; to one portion add 1 cc of acetic acid and 0.5 cc of a saturated bromine water, an immediate discoloration occurs; to the other portion add 0.1 cc of tenth normal potassium permanganate solution, a yellow color appears immediately, turning to brown.

Boil about 0.5 Gm of alurate with 50 cc of water for two minutes, no odor develops, cool and filter, separate portions of 10 cc each of the filtrate, yield no opalescence with 1 cc of diluted nitric acid and 1 cc of silver nitrate solution (chloride), no turbidity with 1 cc of diluted nitric acid and 1 cc of barium nitrate solution (sulfate), no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals). Incinerate about 1 Gm of alurate, accurately weighed, there is not more than 0.1 per cent residue. Dissolve about 0.5 Gm of alurate, accurately weighed, in 25 cc of previously neutralized alcohol, dilute with an equal volume of water previously boiled to remove carbon dioxide, and titrate with tenth normal sodium hydroxide solution using thymolphthalein as an indicator; the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent allyliso propylbarbituric acid.

HOFFMANN-LA ROCHE INC

Alurate (Powder) bulk

Tablets Alurate 65 mg

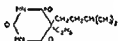
sodium alurate, accurately weighed, to a suitable Squibb separatory funnel add 50 cc of water, followed by addition of 10 cc of diluted hydrochloric acid, extract with eight successive portions of ether of 25 cc each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 90 C the amount of allylisopropyl barbituric acid corresponds to not less than 90 per cent nor more than 91 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath, to the residue obtained add 5 cc of sulfuric acid, heat cautiously until the excess of sulfuric acid has been volatilized repeat twice using portions of 1 cc each of sulfuric acid each time add about 0.5 Gm of ammonium carbonate ignite to constant weight and weight as sodium sulfate the percentage of sodium corresponds to not less than 9 per cent nor more than 10 per cent when calculated to the dried substance

HOFFMANN-LA ROCHE, INC

Capsules Sodium Alurate. 227 Gm Each capsule is equivalent to approximately 0.2 Gm of alurate

U S patent 1 444 802 (Feb 13, 1923, expired) U S trademark 230 059

AMYTAL — 5-Isoamyl-5 ethylbarbituric acid — Isoamyl ethyl malonylurea — $C_{11}H_{19}O_3N_2$ — M W 226.27



Actions and Uses—The actions and uses of amytal resemble those of barbital. It is used as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anesthesia.

Dosage—It is given orally in tablet form with water or hot milk. As a sedative 20 mg to 40 mg two or three times daily. As a hypnotic 0.1 to 0.3 Gm one half to one hour before sleep is desired. For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm, being determined by a large number of factors (age, etc). It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. As an antispasmodic in tetanus 0.4 to 0.8 Gm may be required to control convulsions.

Tests and Standards—

As a sedative 20 mg to 40 mg two or three times daily.
As a hypnotic 0.1 to 0.3 Gm one half to one hour before sleep is desired.
For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm, being determined by a large number of factors (age, etc).
It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use.
As an antispasmodic in tetanus 0.4 to 0.8 Gm may be required to control convulsions.

Dissolve 0.1 Gm of amytal in 1 cc of sulfuric acid the solution is colorless (*readily carbonized substance*) Boil 0.5 Gm of amytal with 50 cc of 1 cc of (chloride barium saturation Incine

does not exceed 0.1 per cent Dissolve about 0.5 Gm of amytal accurately weighed, in 25 cc of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution, using thymolphthalein as an indicator the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of isoamyl ethylbarbituric acid

ELI LILLY AND COMPANY

Amytal (Powder): bulk

U S patent 1,514,573 (Nov 4 1924, expired) U S trademark 161,125

Tablets Amytal: 8 mg, 16 mg, 32 mg 48 mg and 96 mg

Elixir Amytal. 0.44 Gm per hundred cubic centimeters and 0.88 Gm per hundred cubic centimeters in a vehicle containing alcohol, glycerin water and aromatics, methenamine is present for the purpose of increasing the solubility of the amytal

SODIUM AMYTAL—Sodium Isoamylethylbarbiturate—The monosodium salt of 5 isoamyl 5 ethylbarbituric acid— $C_{11}H_{17}O_3N_2Na$ —M W 248.26

Actions and Uses—The actions and uses of sodium amytal resemble those of barbital The product is used as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anesthesia

Dosage—As a potent sedative or hypnotic 0.2 Gm, repeated if necessary at intervals of six hours For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm being determined by a large number of factors (age, etc) As an antispasmodic in tetanus, from 0.4 to 0.8 Gm may be required to control convulsions It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use In some patients barbital derivatives produce restlessness and excitement, and to these patients sodium amytal should not be administered It may be administered by mouth or, if necessary, the same dose may be given rectally, in the form of capsules inserted as suppositories or as powder placed in a little water; it should be administered intravenously only in those conditions outlined in the general section on barbituric acid derivatives

Tests and Standards—

Sodium Amytal powder, soluble in water, Dissolve in an excess of ethylalcohol. Incinerate for sodium of a 25 evolution 10 cc of of mercuric excess of solution. Dissolve 5 cc of of 10 cc 1 cc of of 1 cc sodium acid filtration on about 0.2 Gm of sodium amytal to 1 cc of sulfuric acid the solution is colorless (*readily carbonizable substances*). Transfer about 1 Gm of sodium amytal, accurately weighed, to a glass stoppered cylinder, shake the contents for ten min, filter through filter paper and repeat with ether and utilizing the dryness in a tared beaker residue does not exceed 0.1% (uric acid).

Dry about 1 Gm of sodium amytal, accurately weighed, to constant weight at 90 C. The loss does not exceed 1 per cent. Transfer about 0.5 Gm. of sodium amytal, accurately weighed to a suitable Squibb separatory funnel add 50 cc of water, followed by the addition of 10 cc. of diluted hydrochloric acid extract with eight successive portions of ether, using 25 cc. each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 90 C. to not less than the dried substance foregoing mixture to dryness on a tared beaker and 1 cc of sulfuric acid and 1 cc of water, add about 0.5 Gm. of ammonium carbonate, ignite to constant weight and weigh as sodium sulfate. The percentage of sodium corresponds to not less than 8.9 per cent nor more than 9.5 per cent when calculated to the dried substance.

ELI LILLY AND COMPANY

Sodium Amytal (Powder): 30 cc

U. S. patent 1,514,573 (Nov. 4, 1924, expired) U. S. trademark 161,125

Sodium Amytal 65 mg, 0.125 Gm, 0.25 Gm, 0.5 Gm and 1.0 Gm ampuls. Each ampul of 0.25 Gm, 0.5 Gm and 1.0 Gm is accompanied by an ampul of distilled water.

Pulvules Sodium Amytal. 65 mg and 0.130 Gm

Suppositories Sodium Amytal. 0.130 Gm

DATE: 11/11/11

under Elixir of Barbitals

Actions and Uses—See the preceding article, Barbituric Acid Derivatives. Barbitol is quickly absorbed, especially when it is given in solution. Small doses induce sleep, apparently with little other effect, and are relatively safe, but fatalities have followed its indiscriminate use.

Dosage—As hypnotic, 0.3 Gm, best prescribed in the form of powder to be given in hot fluid, such as hot milk, half an hour or an hour before bedtime. Pills or tablets should be crushed before swallowing, to insure absorption. From 0.1 to 0.15 Gm are used with analgetics for the relief of pain.

ABBOTT LABORATORIES

Tablets Barbitol: 03 Gm

MALLINCKRODT CHEMICAL WORKS

Barbital (Powder): bulk

MERCK & Co., Inc.

Barbital (Powder): bulk

Tablets Barbital • 0.3 Gm

THE WM. S. MERRILL COMPANY

Tablets Barbitol • 0.3 Gm

WINTHROP CHEMICAL COMPANY, INC.

Veronal (Powder): bulk

U S patent 782 739 (Feb 14 1905, expired) U S trademark

Tablets Veronal: 0.3 Gm

Elixir of Veronal: Each 4 cc contains veronal 0.13 Gm in a menstruum containing alcohol 33.5 per cent.

BARBITAL SODIUM.—Soluble Barbitol—Sodium Diethylbarbiturate—Soluble Barbitone—Sodium Diethylmalonylurea—U S P—Medinal—Veronal Sodium— $C_{11}H_{10}O_3N_2Na$ —M W 206.18—“Contains not less than 88 per cent and not more than 90 per cent of barbitol ($C_{11}H_{10}N_2O_3$), calculated on a moisture free basis, the moisture being determined on a separate portion by drying at 100° C for 3 hours” U S P

For description and standards see the U. S. Pharmacopeia under Barbitol Sodium and Barbitol Sodium Tablets.

Actions and Uses—The same as those of barbitol. It is claimed however, that this drug acts more rapidly on account of its greater solubility. Because of its solubility, administration by rectal injection and also subcutaneous injection has been proposed.

Dosage—The same as that of barbitol. It should be administered in aqueous solution.

ABBOTT LABORATORIES

Tablets Barbitol Sodium 0.3 Gm

MERCK & Co., INC

Barbitol Sodium (*Powder*) bulk

Tablets Barbitol Sodium 0.3 Gm

SCHERING & GLATZ, INC

Medinal (*Powder*) 30 Gm bottles

U S patents 780,241 (Jan 17 1905 expired) and 879,499 (Feb 19 1908 expired) U S trademark 269,753

Elixir Medinal 180 cc and 384 liters. A solution containing in each 4 cc 0.12 Gm medinal in 20 per cent alcohol.

Tablets Medinal 0.3 Gm

Suppositories Medinal 0.65 Gm

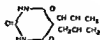
WINTHROP CHEMICAL COMPANY, INC

Veronal Sodium (*Powder*) bulk

U S patent 782,739 (Feb 14 1905 expired) U S trademark 40,115

Tablets Veronal Sodium 65 mg

DIAL — 5,5-Diallylbarbituric acid — Diallylmalonylurea — $C_{11}H_{15}O_3N_2$ — M W 208.21



Actions and Uses—The actions and uses of Dial are essentially similar to those of barbitol but Dial is more active than barbitol and it is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic. Therapeutic doses act on the higher centers of the

those of Dial. It is claimed that the ethyl carbamate and monoethylurea are used as solvents and in the amounts present

does not greatly affect the accuracy of the Dial content. Such a Dial will create a non-probable situation as a simulation and, in the case of a genuine emergency relay, the information is often. The chief problem is only different; what must be noted is that it may be useful.

At a later date, the following information was obtained from the same source:

Text and Notes—

[illegible][illegible][illegible]

Incinerate about 1 gm of B3a accurately weighed the residue does not exceed 0.5 per cent. It must be about 0.5 gm, accurately weighed in 25 cc of previously heated and acidified dilute with an equal volume of water and a trace with tooth powder and in hydrochloric acid using thymol blue as an indicator the amount of tooth powder and in hydrochloric acid it consumes a quantity is not less than 9.5 per cent, or more than 10.5 per cent of diethylthiostyric acid.

CHIA PHARMACEUTICAL PRODUCTS, INC.

Dial (Powder): 10 Gm and 120 Gm

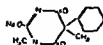
Tablets Dial: 30 mg and 101 Gms

Elizant Dial* Each 4 cc contains 50 mg in a menstruum containing alcohol 25 per cent

Sterile Solution Dial with Urethane: 1 cc and 2 cc ampuls. Each cubic centimeter contains Dial 01 Gm ethyl carbamate (urethane) 0.4 Gm., monoethylurea 0.4 Gm. and water q. s.

U S patent 1 042,265 (Oct 22 1912 expired) U S trademark
93 304 and 126 043

HEXOBARBITAL SOLUBLE

 $C_{11}H_{15}O_3N_2Na - M \quad W \quad 258.25$ 

Actions and Uses—The actions and uses of hexobarbital soluble are essentially similar to those of pentobarbital sodium except that it is designed only for intravenous use to produce anesthesia of short duration. When injected intravenously it is a quick acting, general anesthetic with an early recovery period. In the majority of cases consciousness is restored in from fifteen to thirty minutes, depending on the amount of drug injected. Not uncommonly there follows some drowsiness or sleep if the patient is left undisturbed. While the intravenous use of barbiturates is a valuable procedure under certain circumstances it should be undertaken only by those experienced in this field. It should not be looked on as a routine office procedure, adequate facilities should be at hand to combat untoward reactions. Ataxia and transient amnesia may occasionally be encountered. Contraindications are in general those of the barbital compounds and general anesthetics.

Dosage—As there is considerable variation in individual reactivity to any of the barbiturates, the dose must be individualized. In general, 2 cc. to 4 cc. of a 10 per cent solution is required to induce unconsciousness in adults, this is injected intravenously at the rate of 1 cc. per ten seconds. An additional 1 cc. or 2 cc. may be necessary if relaxation is not obtained with the initial dose, or it may be required during the operative procedure. A total amount of 10 cc. of this 10 per cent solution is seldom required for adults, and it cannot be exceeded without danger.

Caution If the solution is discolored or shows the presence of undissolved particles, even though it is freshly prepared, it should be discarded. The powder and solution undergo change on exposure to air and should not be kept for future use.

Tests and Standards—

Hexobarbital soluble occurs as a white crystalline odorless, hygroscopic powder, with a slightly bitter taste, very soluble in water, freely soluble in alcohol, practically insoluble in ether. An aqueous solution of hexobarbital soluble is alkaline to litmus.

Dissolve about 0.3 Gm. of hexobarbital soluble in 100 cc. of water, add an excess of diluted hydrochloric acid, mix, allow to stand fifteen minutes and collect the resultant cyclohexenylidimethyl barbituric acid on a filter, wash with water and dry at 65° C., it melts at 143-146° C.

Transfer about 0.1 Gm. of the dried cyclohexenylidimethyl barbituric acid to a stoppered cylinder, add 25 cc. of water, shake the mixture for one minute, filter through paper and divide into two portions. To one portion add 1 cc. of acetic acid and 0.5 cc. of water, saturated with

bromine an immediate discoloration occurs, to the other portion add 0.1 cc of tenth normal potassium permanganate solution a pale brownish yellow color appears

Transfer about 0.5 Gm of hexobarbital soluble to a 50 cc Erlenmeyer flask, add 5 cc of water and about 0.4 Gm of *p*-nitrobenzyl chloride dissolved in 10 cc of 90 per cent ethyl alcohol. Attach the flask to a reflux condenser and heat the mixture on a water bath for one half hour. Cool the flask and collect the precipitate on a filter, wash with water, dry at 65 C., dissolve the dry product in just sufficient hot 60 per cent alcohol cool and collect the precipitate, dry at 65 C. the melting point of the product is 113-115 C.

Transfer about 0.3 Gm of hexobarbital soluble to a test tube containing 2 cc of water and add dropwise a saturated solution of bromine in water until the color of bromine faintly persists after vigorously shaking the test tube. Pour the contents of the test tube into 100 cc of water, filter through paper, wash with water and dry at 65 C. the melting point of the product lies between 130 and 132 C., with decomposition.

Incinerate about 1 Gm of hexobarbital soluble in a porcelain dish cool dissolve the residue in 50 cc of water and divide into two portions the first portion responds to tests for sodium carbonate. Rinse the porcelain dish with 2 cc of diluted hydrochloric acid add the rinsings to the second portion and filter through paper the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals).

Transfer about 0.5 Gm of hexobarbital soluble to a 50 cc Erlenmeyer flask add 5 cc of diluted nitric acid allow to stand for fifteen minutes and filter through paper separate portions of 10 cc each of the filtrate yield no opalescence on the addition of 1 cc of silver nitrate solution (chloride), no turbidity on the addition of 1 cc of barium nitrate solution (sulfate).

Dissoiva about 0.5 Gm of hexobarbital soluble in 50 cc of water add 5 cc of diluted nitric acid allow to stand for fifteen minutes and filter through paper separate portions of 10 cc each of the filtrate yield no opalescence on the addition of 1 cc of silver nitrate solution (chloride), no turbidity on the addition of 1 cc of barium nitrate solution (sulfate).

Add about 0.1 Gm of hexobarbital soluble to 2 cc of sulfuric acid the solution is pale yellow, gradually changing to brown-orange (easily carbonisable substances).

The *pn* of a 10 per cent solution of hexobarbital soluble lies between 11 and 12. Dry about 1 Gm of hexobarbital soluble accurately weighed to constant weight at 65 C. the loss in weight is negligible.

Transfer about 0.5 Gm accurately weighed of the dried hexobarbital soluble to a tared porcelain dish add 2 cc of sulfuric acid, cautiously ignite until the excess of sulfuric acid has been volatilized, repeat the ignition twice with the addition of 1 cc of sulfuric acid, add about 0.5 Gm of ammonium carbonate, ignite to constant weight and weigh as sodium sulfate the percentage of sodium corresponds to not less than 8.5 nor more than 9.4 when calculated to the dried substance.

Transfer to a tared porcelain dish of 10 succesor of 10 tared weight correct calcula

cool in ice with an occasional swirling for twenty minutes. Then add

10 cc of 10 per cent potassium iodide solution (iodate free) and allow to stand for ten minutes. Titrate the free iodine with tenth normal sodium thiosulfate solution. When the titration is nearly complete add 5 cc of chloroform using starch solution as the indicator, and continue the titration until colorless. Each cc of tenth normal bromide bromate solution is equivalent to 0.0129 Gm of hexobarbital soluble the amount found corresponds to not less than 99 per cent nor more than 101 per cent.

WINTHROP CHEMICAL COMPANY, INC

Evipal Soluble. 0.5 Gm and 1 Gm powder in ampuls packaged with or without sterile distilled water

U S patent 1947 944 U S trademark 315 515

IPRAL CALCIUM — *Probarbital Calcium* — Calcium 5 ethyl 5 isopropylbarbiturate — The trihydrated calcium salt of 5 ethyl-5 isopropylmalonyl urea ($C_{12}H_{18}O_4N_2$) $Ca \cdot 3H_2O$ — M W 488.58

Actions and Uses — Ipral calcium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours.

Ipral calcium is used as a hypnotic to combat restlessness irritability and sleeplessness. It is claimed that tolerance to ipral calcium is not developed readily, but that its action is so persistent that a patient frequently sleeps on the night succeeding that when the hypnotic was administered.

Dosage — From 0.12 to 0.25 Gm followed by a cupful of hot water, tea or milk.

Tests and Standards —

Ipral calcium occurs as a white crystalline odorless powder with a slightly bitter taste. It is soluble in about 40 parts of water at 25 C insoluble in alcohol. An aqueous solution is alkaline in reaction to litmus. Add 0.2 Gm to 20 cc of water acidify with 5 cc diluted hydrochloric acid filter make filtrate ammoniacal then add 2 cc of ammonium oxalate solution a precipitate forms insoluble on addition of acetic acid in excess but soluble on the addition of hydrochloric acid. Wash well the residue from the foregoing with water dry at 100 C the melting point should be from 200 to 203 C. To 0.05 Gm of residue add 2 cc sodium hydroxide solution the residue dissolves. Place 2 Gm in a glass stoppered flask treat with 25 cc of carbon dioxide free water and agitate occasionally over a period of two hours by decantation separate the insoluble material transfer the insoluble residue to a test tube treat with diluted sulfuric acid and pass the emitted gases into 20 cc of barium hydroxide solution not more than a barely perceptible turbidity should result (*limit of carbonate*). Dry about 1 Gm accurately weighed to constant weight at 100 C the loss does not exceed 12 per cent. Transfer about 1 Gm., accurately weighed to a flask and shake the contents through filter respectively, of ether and dry to weigh more than 10 cc (10 cc of 10% acid). Dissolve in 10 cc of water and add 10 cc of ether, allow the solvent to evaporate spontaneously, dry the residue to

constant weight at 100 C., and weigh the weight of ethylisopropyl barbituric acid is not less than 78.5 per cent, nor more than 83.0 per cent. Ignite about 1 Gm. accurately weighed, cool, treat the residue with 5 cc. diluted hydrochloric acid, transfer to a 250 cc. beaker, add 25 cc. water and ammonia water until ammoniacal, warm, add 20 cc. boiling ammonium oxalate solution, boil and allow to stand overnight, collect the precipitate on an ashless filter paper, wash with diluted ammonia water (1 part of ammonia water to 5 parts of water), transfer the precipitate to a platinum crucible, and ignite to constant weight; the weight of calcium oxide corresponds to not less than 8.0 per cent, nor more than 8.5 per cent calcium.

E. R. SQUINN & SONS

Tablets Ipral Calcium: 50 mg. and 0.13 Gm.

U. S. patents 1,255,951 (Feb. 12, 1918, expired), 1,576,014 (March 9, 1926, expired) U. S. trademark 208,813

IPRAL SODIUM.—Probarbital Sodium—Sodium 5-ethyl-5-isopropylbarbiturate—The sodium salt of 5-ethyl-5-isopropylmalonylhrea— $C_8H_{12}O_4N_2Na$ —M. W. 220.21



Actions and Uses.—Ipral sodium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours.

Ipral sodium is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to ipral sodium is not developed readily, and that its action is persistent.

Dosage.—From 0.12 to 0.25 Gm. followed by a cupful of hot water, tea or milk.

Tests and Standards—

Caution. Aqueous solutions of ipral sodium are not stable but decompose on standing; on boiling, a precipitation occurs.

Ipral sodium is a white hygroscopic powder, soluble in water, slightly soluble in alcohol and practically insoluble in ether and chloroform. An aqueous solution of ipral sodium has an alkaline reaction to litmus. Dissolve about 0.5 Gm. of ipral sodium in 100 cc.

an excess of ammonia.

Dissolve about 0.5 Gm. of ipral sodium in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper. Separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*), no turbidity on the addition of 1 cc. of barium nitrate solution (*sulfate*). To about 0.2 Gm. of ipral sodium in 25 cc. of water, add 1 cc. of diluted hydrochloric

acid filter through paper the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals). Add about 0.1 Gm. of ipral sodium to 1 cc. of sulfuric acid the solution is colorless (readily carbonizable substances).

Transfer about 1 Gm of ipral sodium accurately weighed to a glass stoppered cylinder add 50 cc of anhydrous ether stopper and shake for ten minutes decant the supernatant liquid through filter paper and repeat twice using 25 cc and 15 cc portions respectively of ether utilizing the same filter evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90 C. the residue does not exceed 0.2 per cent (uncombined ethylisopropyl barbituric acid).

Dry about 1 Gm of ipral sodium accurately weighed to constant weight at 100 C. the loss does not exceed 2 per cent. Transfer about 0.5 Gm of ipral sodium accurately weighed to a suitable Squibb separatory funnel add 50 cc. of water followed by addition of 10 cc of diluted hydrochloric acid extract with eight successive portions of ether of 25 cc each evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 100 C. the amount of ethylisopropyl barbiturate calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath to the residue obtained, add 5 cc of sulfuric acid heat cautiously until the excess of sulfuric acid has been volatilized repeat twice using portions of 1 cc each of sulfuric acid each time add about 0.5 Gm of ammonium carbonate ignite to constant weight and weigh as sodium sulfate the percentage of sodium corresponds to not less than 9.5 per cent nor more than 11.5 per cent when calculated to the dried substance.

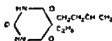
L. R. SQUIBB & SONS

Elixir Ipral Sodium 13 Gm in 1000 cc 5 cc is equivalent to 65 mg of ipral sodium

Tablets Ipral Sodium 0.25 Gm

U. S. patents 1255951 (Feb 12 1918 expired) and 1576014 (March 9 1926 expired) U. S. trademark 208813

NEONAL—5 *n* Butyl 5 ethylbarbituric acid — 5 *n* Butyl 5 ethylmalonylurea — $C_{18}H_{21}O_4N_2$ — M. W. 212.24



Actions and Uses—The actions and uses of neonol are essentially similar to those of barbitol but it is about three times as active as the latter hence it is used in correspondingly smaller doses. It is claimed that it exerts a sedative action to an exceptional degree, and that it is useful therefore in high nervous tension, neuroses and other conditions in which a sedative is required.

Dosage—From 50 mg to 0.4 Gm. For mild insomnias 50 mg to 0.1 Gm is stated ordinarily to produce sleep. A dose of 0.4 Gm is the maximum dose which should be required in the course of twenty-four hours administered in divided doses.

Tests and Standards—

Neonal occurs as a white crystalline, odorless powder, with a slightly bitter taste readily soluble in alcohol about 1 in 5 and ether about 1 in 10, very slightly soluble in cold water insoluble in the paraffin

portion add 5 cc of silver nitrate solution a white precipitate results soluble in 5 cc of ammonia water Boil 0.5 Gm with 5 cc of a 25 per cent sodium hydroxide solution it is decomposed with the evolution of ammonia.

Dissolve 0.1 Gm in 1 cc of sulfuric acid the solution is colorless (readily carbonizable substances) Boil 0.5 Gm with 50 cc water for two minutes no odor develops, cool and filter separate portions of 10 cc each of the filtrate yield no opalescence with 1 cc of diluted nitric acid and 1 cc of silver nitrate solution (chloride) no turbidity (sulfate) no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals)

Incinerate about 1 Gm accurately weighed the residue does not exceed 0.1 per cent

Dissolve about 0.5 Gm accurately weighed in 25 cc of previously neutralized alcohol dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution using thymolphthalein as an indicator the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of butylethylbarbituric acid

ABBOTT LABORATORIES

Neonal (Powder): bulk

U S patent 1 607 520 (Dec 7 1926 expired) U S trademark 175 580

Tablets Neonal 0.1 Gm

NOSTAL—5 Isopropyl 5 β bromallyl barbituric acid—5 isopropyl 5 β bromallyl malonylurea— $C_{15}H_{13}O_2N_2Br$ —M W 289.14



*Actions and Uses—*The actions and uses of nostal are essentially similar to those of barbital but nostal is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as an hypnotic

*Dosage—*As a sedative 50 mg to 0.1 Gm. As an hypnotic 0.1 to 0.3 Gm, for children, 50 mg to 0.1 Gm according to age. Nostal should be administered preferably with a hot drink

Tests and Standards—

Nostal occurs as a colorless crystalline odorless powder, with a slightly bitter taste readily soluble in alcohol glacial acetic acid and acetone, sparingly soluble in ether, chloroform benzene and water. A saturated aqueous solution is acid to litmus paper. Nostal melts at 177-179 C

Fuse about 0.1 Gm of nossal and 1 Gm of crushed potassium hydroxide previously moistened with 1 cc of alcohol in a nickel crucible it is decomposed with the evolution of ammonia, cool dissolve the residue in 10 cc of water, add 10 cc of diluted nitric acid filter through paper, to the filtrate add 5 cc of silver nitrate solution a curdy, dirty white precipitate results, soluble in a large excess of stronger ammonia water. Place approximately 0.3 Gm of nossal in a 25 cc glass stoppered cylinder add a mixture of 1 cc normal sodium hydroxide solution and 5 cc of water, shake the contents for one minute, filter through paper and divide into two portions to one portion add 1 cc of mercuric chloride solution a white precipitate results, soluble in 10 cc of ammonia water, to the other portion add 5 cc of silver nitrate solution a white precipitate results, soluble in 5 cc of ammonia water.

Boil about 0.5 Gm of nossal with 50 cc of water for two minutes, no odor develops, cool and filter separate portions of 10 cc each of the filtrate yield no opalescence with 1 cc of diluted nitric acid and 1 cc of silver nitrate solution (*soluble halides*) no turbidity with 1 cc of diluted nitric acid and 1 cc of barium nitrate solution (*sulfate*), no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm of nossal accurately weighed the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm accurately weighed, in 25 cc of previously neutralized alcohol dilute with an equal volume of water and titrate with tenth normal sodium hydroxide

nor more than 2/9 per cent

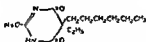
RIEDEL-DE HAEN DIVISION OF AMES COMPANY, INC

Nossal (Powder): bulk

U S patent 1 622 129 (March 22, 1927 expired) U S trademark 270 750

Tablets Nossal 0.1 Gm

ORTAL-SODIUM.—Sodium 5-*n*-hexyl 5-ethyl barbiturate—Sodium *n*-hexylethyl malonylurea—The monosodium salt of 5-*n*-hexyl 5-ethyl barbituric acid— $C_{21}H_{33}O_4N_2Na$ —M W 262.29



Actions and Uses.—The actions and uses of ortal sodium are essentially similar to those of barbital, but ortal sodium is more active than barbital and it is used in correspondingly smaller doses.

Dosage.—From 0.2 to 0.4 Gm followed by a glass of water. It is rarely necessary to give more than 1 Gm in twenty-four hours. When oral administration is contraindicated, ortal sodium may be administered rectally.

Caution. Aqueous solutions of ortal-sodium are not stable but decompose on standing, on boiling, a precipitation occurs with evolution of ammonia.

Tests and Standards—

Ortal sodium is an odorless, white or slightly yellowish powder, with a bitter taste very soluble in water, soluble in alcohol practically insoluble in ether and benzene. An aqueous solution of ortal sodium has an alkaline reaction to litmus.

Dissolve about 0.5 Gm of ortal sodium in 100 cc of water, add an excess of diluted hydrochloric acid, collect the resultant hexylethyl barbituric acid on a filter, wash and dry at 90° C; it melts at 122-125° C. Incinerate about 1 Gm of ortal sodium; the residue responds to tests for sodium carbonate. Boil about 0.5 Gm of ortal sodium with 5 cc of a 25 per cent sodium hydroxide solution; it is decomposed with evolution of ammonia.

of water and divide in
mercuric chloride solut
excess of ammonia to
solution a white precip

Dissolve about 0.5 G
of diluted nitric acid
10 cc each of the filtr
of 1 cc of silver nitr
tent normal hydrochlor
bidity on the addition of 1 cc of barium nitrate solution (sulfate).
To about 0.2 Gm of ortal sodium in 25 cc of water, add 1 cc of
diluted hydrochloric acid; filter through paper; the filtrate yields no
coloration or precipitation on saturation with hydrogen sulfide (sulfide
cc of sul
substances)

Dry about 1 Gm of ortal sodium accurately weighed to constant weight at 100° C; the loss does not exceed 2.5 per cent. Transfer about 0.5 Gm of ortal sodium accurately weighed to a suitable Squibb separatory funnel; add 50 cc of water followed by 10 cc of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc each; evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 90° C; the amount of hexyl barbituric acid corresponds to not less than 90.8 per cent.

weigh as sodium sulfate; the percentage of sodium corresponds to not less than 8.5 per cent nor more than 9 per cent when calculated to the dried substance.

PARKE, DAVIS & COMPANY

Capsules Ortal Sodium 50 mg 0.2 Gm 0.3 Gm

U. S. patent 1,624,546 (April 12, 1927 expired) U. S. trademark 302,616

PENTOBARBITAL SODIUM—Soluble Pentobarbital
Contains not less than 90 per cent and not more than 92 per cent of pentobarbital ($C_{11}H_{12}N_2O_4$) calculated on a moisture free basis, the moisture being determined on a separate portion by drying at 90° C for six hours. U. S. P.

For description and standards see the U S Pharmacopeia under Pentobarbital Sodium Pentobarbital Sodium Capsules and Pentobarbital Sodium Tablets

Actions and Uses—The actions and uses of pentobarbital sodium are essentially similar to those of barbitol but it is effective in smaller doses. It may be administered by mouth and rectum and may be injected intravenously (see general article on barbituric acid derivatives). The action is of relatively brief duration which may constitute an advantage especially when relatively large doses are administered. It is used as a sedative particularly prior to local general or spinal anesthesia. It can be used safely for such purposes only by those who have had adequate experience and who are familiar with the literature concerning such use.

Dosage—Orally as hypnotic 0.1 Gm. as preanesthetic sedative 0.2 Gm. Rectally for analgesia for infants up to 1 year 30 mg. up to 3 years 60 mg. for adults 0.32 to 0.38 Gm. dissolved in a few cubic centimeters of water. Average intravenous dose for adults has been 0.2 to 0.3 Gm. for children has not been definitely decided although a child 6 to 12 years may receive up to 0.1 to 0.2 Gm.

Caution Aqueous solutions of pentobarbital sodium are not stable but decompose on standing on boiling a precipitation occurs with evolution of ammonia.

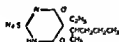
LAKESIDE LABORATORIES INC.

Solution Pentobarbital Sodium and Benzyl Alcohol 1 cc and 2 cc ampuls. Each cubic centimeter contains 0.162 Gm. of pentobarbital sodium and 20 mg. of benzyl alcohol dissolved in propylene glycol.

ELI LILLY & COMPANY

Pentobarbital Sodium 0.5 Gm. marketed in ampuls with or without a 10 cc. size ampul of distilled water.

PENTOTHAL SODIUM—Sodium 5 ethyl 5 (1 methyl butyl) thiobarbiturate. The monosodium salt of 5 ethyl 5 (1 methylbutyl) thiobarbituric acid— $C_{11}H_{19}O_3N_2SNa$ —M. W. 264.32



See also description of pentothal sodium sodium except s and the action acting general / be emphasized

that the intravenous use of barbiturates may be a valuable procedure, but such use is potentially dangerous and should be undertaken only by experts for short operations. The use of pentothal sodium is not recommended in major operative procedures requiring long anesthesia or for office procedures. It should be employed only by competent experienced anesthetists or surgeons who have at their hands facilities to combat problems involving respiratory depression and carbon dioxide oxygen balance.

Dosage—Two or three cc of a 5 per cent solution is injected in about ten or fifteen seconds. The injection is then stopped to permit the complete effect to appear, which requires from thirty to thirty five seconds. If relaxation has not occurred, an additional 2 or 3 cc may be injected at the same rate as before.

Caution Aqueous solutions of pentothal sodium are not stable but decompose on standing, on boiling, a precipitation occurs.

Tests and Standards—

Pentothal sodium occurs as a yellowish white hygroscopic powder possessing a sulfur like odor soluble in water and alcohol insoluble in an aqueous solution.

1 cc of water, add 1 cc of dilute hydrochloric acid, wash and dry at 60°C. 1 Gm of pentothal sodium the residue responds to tests for sodium carbonate and very faintly for sulfide. Boil about 0.2 Gm of pentothal sodium with 25 per cent sodium hydroxide solution no evolution of ammonia occurs. Dissolve about 0.1 Gm of pentothal sodium in 10 cc of water add 1 cc of mercuric chloride a white precipitate results soluble in an excess of ammonia.

Dissolve about 0.5 Gm of pentothal sodium in 50 cc of water, add 5 cc of diluted nitric acid and filter through paper separate portions of 10 cc each of the filtrate yield a faint opalescence on the addition of 1 cc of silver nitrate solution (chloride), very slight turbidity on the addition of 1 cc barium nitrate solution (sulfate). To about 0.2 Gm

tions to dryness in a stream of warm air and dry to constant weight at 70°C. The amount of ethyl (1-methylbutyl) thiobarbituric acid corresponds to not less than 89 per cent nor more than 92 per cent calculated to the dried substance.

Transfer the acidulated aqueous portions from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath. To the residue obtained add 5 cc of sulfuric acid heat cautiously until the excess of sulfuric acid has been volatilized repeat twice using portions of 1 cc each of sulfuric acid each time add about 0.5 Gm of ammonium carbonate ignite to constant weight and weigh as sodium sulfate. The percentage of sodium corresponds to not less than 85 per cent nor more than 88 per cent when calculated to the dried substance.

Pentothal sodium with anhydrous sodium carbonate

It occurs a like odor an sodium has a ρ_n of 10.4. Dissolve al carbonate in acid; collect a filter paper 0.2 Gm of 25 per cent. Dissc carbona through faint opalescence on the addition of 1 cc. of silver nitrate solution (chloride), very slight turbidity on the addition of 1 cc barium nitrate solution (sulfate). To about 0.2 Gm of pentothal sodium with anhydrous sodium carbonate in 25 cc of water add 1 cc of diluted hydrochloric acid, filter through paper; the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals).

Dry about 0.5 Gm of pentothal sodium with anhydrous sodium carbonate, accurately weighed, at 70 C., for twenty four hours. the loss in weight should not exceed 2 per cent. Transfer about 0.3 Gm of pentothal sodium with anhydrous sodium carbonate, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc of water, followed by the addition of 10 cc of diluted hydrochloric acid, extract with six successive portions of chloroform using 25 cc, 25 cc, 20 cc, 15 cc, 15 cc and 10 cc, respectively, evaporate the combined chloroformic extraction to dryness in a stream of warm air and dry to constant weight at 70 C. the percentage of ethyl (1 methylpropyl carbonyl) thiobarbituric acid should correspond to not less than 84 per cent nor more than 87 per cent when calculated to the dried substance.

Transfer the acidulated aqueous portions from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath, to the residue obtained add 5 cc of sulfuric acid, heat cautiously until the excess of sulfuric acid has been volatilized, repeat twice, using 1 cc portions of sulfuric acid each time, add about 0.5 Gm of ammonium carbonate, ignite to constant weight and weigh as sodium sulfate the percentage of sodium corresponds to not less than 10.0 per cent nor more than 10.7 per cent when calculated to the dried substance.

Transfer the acidulated aqueous portions from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath, to the residue obtained add 5 cc of sulfuric acid, heat cautiously until the excess of sulfuric acid has been volatilized, repeat twice, using 1 cc portions of sulfuric acid each time, add about 0.5 Gm of ammonium carbonate, ignite to constant weight and weigh as sodium sulfate the percentage of sodium corresponds to not less than 10.0 per cent nor more than 10.7 per cent when calculated to the dried substance.

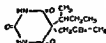
Transfer the acidulated aqueous portions from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath, to the residue obtained add 5 cc of sulfuric acid, heat cautiously until the excess of sulfuric acid has been volatilized, repeat twice, using 1 cc portions of sulfuric acid each time, add about 0.5 Gm of ammonium carbonate, ignite to constant weight and weigh as sodium sulfate the percentage of sodium corresponds to not less than 10.0 per cent nor more than 10.7 per cent when calculated to the dried substance.

ABBOTT LABORATORIES

Pentothal Sodium: 0.5 Gm and 1.0 Gm ampuls with 30 mg and 60 mg anhydrous sodium carbonate respectively, as buffer, 50 Gm multiple dose ampul with 0.3 Gm, anhydrous sodium carbonate as a buffer.

U S patent 2,153,729 (April 11, 1939, expires 1956). U S trade mark 334,340

PERNOSTON.—5-sec butyl-5- β -bromallyl barbituric acid.—5-(butyl-2)-5- β -brompropenyl malonylurea— $C_{11}H_{15}O_3N_2Br$.—M W. 303.16



Actions and Uses.—The actions and uses of pernoston are essentially similar to those of barbitol, but pernoston is more active than barbitol and is used in correspondingly smaller

doses. It is promptly absorbed and is rapidly changed and destroyed within the body. It is used in combating insomnia due to emotional strain and nervous instability.

Dosage—One tablet (194 mg) given one half hour before sleep is desired preferably followed by a glass of warm milk or lemonade. For hypnosis in the presence of pain one tablet given in conjunction with acetylsalicylic acid.

Tests and Standards.—

Pernoston occurs as a fine white, crystalline powder, with a slightly bitter taste, completely soluble in alcohol and ether, very slightly soluble in cold water, insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Pernoston melts at 130 to 133 C.

Place approximately 1 Gm of pernoston in a 25 cc. glass stoppered cylinder add 10 cc of water and 1 cc. of sodium hydroxide solution and shake for one minute. Filter through paper and divide into two portions, to one portion add 1 cc of mercury bichloride solution a white precipitate results soluble in 10 cc of ammonia water, to the other portion add 5 cc of silver nitrate solution a white precipitate results, soluble in 5 cc of ammonia water.

Fuse about 0.1 Gm of pernoston and 1 Gm of crushed potassium hydroxide previously moistened with 1 cc of alcoholic potassium hydroxide solution in a nickel crucible it is decomposed with the evolution of ammonia, cool dissolve the residue in 10 cc of water, add 10 cc of diluted nitric acid filter through paper to the filtrate add 5 cc of silver nitrate solution a curdy dirty white precipitate results soluble in excess of stronger ammonia water.

Dissolve 0.1 Gm of pernoston in 1 cc of sulfuric acid, the liquid assumes a yellow color, changing slowly to a brownish red, finally to a dark red. Place 1 Gm of pernoston in a 25 cc glass stoppered cylinder add 10 cc. of water shake for one minute, filter through paper and divide into two portions to one portion add 0.5 cc of a saturated bromine water an immediate discoloration occurs, to the other portion add 0.1 cc of tenth normal potassium permanganate a yellow color appears immediately.

Boil 0.5 Gm of pernoston with 50 cc of water for two minutes no color develops, cool and filter, separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc of diluted nitric acid and 1 cc of silver nitrate solution (*chloride*) no turbidity with 1 cc of diluted nitric acid and 1 cc of barium nitrate solution (*sulfate*) no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Inclinate about 1 Gm of pernoston accurately weighed the residue does not exceed 0.1 per cent. Transfer about 0.25 Gm. of pernoston accurately weighed to a bomb tube determine the bromine content by the Carius method the amount of bromine found should be not less than 26.1 per cent nor more than 26.6 per cent. Dissolve about 0.5 Gm of pernoston accurately weighed in 25 cc of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution using thymolphthalein as an indicator, the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of *sec* butyl bromallyl barbituric acid.

REDACTED OF MAIN DIVISION OF AMES COMPANY, INC

Pernoston (Powder): Bulk

U S patent 1739662 (Dec. 17, 1929, expires 1946) U S trade mark 330815

Tablets Pernoston• 194 mg

PERNOSTON SODIUM.—*See also* *Pharmacopoeia*

M. W. 325.15.

Actions and Uses.—The action of pernoston sodium is like that of pernoston except that the effects are induced almost immediately after its intravenous injection. It is used when the oral administration of a barbiturate is not feasible either because of interference with swallowing and when prompt action is imperative, as in the presence of convulsions. The effects are delayed for from thirty to forty-five minutes after the intramuscular injection. The intravenous use demands the rigid observance of the proper technic. The contraindications are important.

Dosage.—One cc. of the 10 per cent solution (in ampuls) per 125 Kg. of body weight injected intravenously at the rate of 1 cc. total per minute until the patient sleeps or until the full dose has been injected. The intramuscular dose is the same as that by vein, but it may be injected at once. Ampuls containing a deposit should not be used.

Tests and Standards—

*Pernoston sodium occurs as a fine, white, crystalline powder, possessing a bitter taste, soluble in water and alcohol, slightly soluble in ether and chloroform. A 10 per cent aqueous solution is alkaline to litmus and phenolphthalein and has a *pn* of approximately 9.5.*

Transfer 5 cc. of a 10 per cent solution of pernoston sodium to a test tube, add 2 cc. of diluted hydrochloric acid, allow the precipitate to crystallize, filter, wash and recrystallize from an ethanol-water mixture; the melting point of the pernoston is from 130 to 133 C.

Transfer 5 cc. portions of a 10 per cent solution of pernoston sodium to two test tubes and to one add 1 cc. of mercury bichloride solution; a white precipitate results, soluble in 10 cc. of ammonium hydroxide, to the other portion add 5 cc. of silver nitrate solution; a white precipitate results, soluble in 5 cc. of ammonium hydroxide.

Dissolve 0.1 Gm. of pernoston sodium in 1 cc. of sulfuric acid; the liquid assumes a yellow color, changing to brownish red and finally to dark red. Acidify 40 cc. of a 10 per cent solution of pernoston sodium with diluted nitric acid and filter, separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of silver nitrate solution (*chloride*), no turbidity with 1 cc. of barium nitrate solution (*sulfate*), no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Transfer about 0.5 Gm. of pernoston sodium, previously dried and accurately weighed, to a tared porcelain dish and add 2 cc. of sulfuric acid, evaporate the excess acid, ash the residue and ignite at 900 C. the weight of sodium sulfate is not less than 21.4 per cent nor more than 22.2 per cent. Transfer about 0.3 Gm. of pernoston sodium, dried and accurately weighed, to a bomb tube and determine the bromine content by means of the Carius method; the bromine found is not less than 24.3 per cent nor more than 24.8 per cent. Transfer a sample of pernoston sodium, dried and accurately weighed, to a kjeldahl flask and digest with sulfuric acid in the presence of selenium, dilute, make alkaline, distill into standard acid and titrate the excess acid with standard alkali; the nitrogen content is not less than 8.3 per cent nor more than 8.8 per cent.

RIEDER DI RAIN DIVISION OF AMES COMPANY, INC.

Solution Pernoston Sodium, 10%, 2 cc. ampuls

U S patent 1739 662 (Dec. 17 1929 expires 1946) U S trade mark 330 845

PHANODORN—Cyclobarbital—Cyclohexenyl ethyl barbituric acid— $5\Delta^6$ -cyclohexenyl 5 ethyl malonylurea— $C_{14}H_{18}O_4N_2$ —M W 236.26



Actions and Uses—The actions and uses of phanodorn resemble those of barbital. It is eliminated more rapidly than barbital, hence the action is not so lasting. This is an advantage when it is used merely to put one to sleep and sleep will then continue without its further action. It is used mainly for its sedative action in neurasthenia, psychoses, and various types of insomnia.

Dosage—For the mildest type of simple insomnia, 0.1 Gm. or $\frac{1}{2}$ tablet. In intractable or obstinate insomnia, from 0.2 to 0.4 Gm. or one to two tablets. The larger dose should not be repeated within less than twelve hours. The average dose is 0.2 Gm. or one tablet.

Tests and Standards—

Phanodorn occurs as a white crystalline, odorless powder, with a bitter taste, readily soluble in alcohol about 1 in 5 and ether, about 1 in 10, very slightly soluble in benzene and cold water. A saturated aqueous solution is acid to litmus paper. It melts at 171-174 C.

Dissolve 0.1 Gm. in 1 cc. of sulfuric acid; the liquid assumes a yellow color, changing quickly to orange and finally to red. Place 0.3 Gm. in a 25 cc. glass stoppered cylinder, add 1 cc. normal sodium hydroxide solution and 5 cc. water; shake the contents for one minute; filter through paper and divide into two portions: the solution yields a white precipitate with 1 cc. of mercuric chloride solution soluble in 5 cc. of ammonia water; the solution yields a white precipitate with 2 cc. of silver nitrate solution soluble in 5 cc. of ammonia water. Boil 0.5 Gm. with 5 cc. of a 20 per cent sodium hydroxide solution; it is decomposed with the evolution of ammonia.

Boil 0.5 Gm. with 40 cc. of water for two minutes; no odor develops; cool and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (chloride); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (sulfate); no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals).

Incinerate about 1 Gm., accurately weighed; there is not more than 0.01 per cent residue.

Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution using thymolphthalein as an indicator; the amount of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent.

WINTHROP CHEMICAL COMPANY, INC

Tablets Phenodorn 194 mg

U S patent 1 620 796 (Nov 6 1928 expired)

PHENOBARBITAL—Phenylethylmalonylurea — Pheno-
barbitone—U S P—LuminalFor description and standards see the U S Pharmacopeia
under Phenobarbital Phenobarbital Tablets and Elixir of
Phenobarbital*Actions and Uses*—The introduction of the phenyl group
increases the hypnotic and sedative action of phenobarbital over
that of barbitol The toxicity appears to be increased in about
the same ratio The sleep may be preceded by a period of
excitement Moderately large therapeutic doses sometimes cause
severe circulatory depression The formation of a habit has
been reportedPhenobarbital has a sedative action on respiration lessening
the frequency of breathing It is eliminated by the kidneys a
certain portion being probably decomposed in the organism
No gastric disturbances have been observedPhenobarbital is used as a useful hypnotic in nervous insomnia
and conditions of excitement of the nervous system its chief
use in this field is as a sedative and as an antispasmodic in
the treatment of epilepsy in which it lessens the frequency and
severity of seizures Its use as a sedative has also been pro-
posed in chorea neurasthenia cardiac and gastric neuroses
climacteric disorders dysmenorrhea exophthalmic goiter, and
preoperative and postoperative cases*Dosage*—From 15 mg to 0.2 Gm increased if necessary to
0.6 Gm The average dose is 0.1 Gm A maximum dose of
0.6 Gm should not be exceeded**ABBOTT LABORATORIES**Phenobarbital (*Powder*) bulk

Tablets Phenobarbital 16 mg 325 mg, 0.1 Gm

AMERICAN PHARMACEUTICAL COMPANY, INC

Tablets Phenobarbital 32 mg 16 mg and 0.1 Gm

GEORGE A. BREON & COMPANY, INC

Tablets Phenobarbital 32.4 mg and 109 mg

BUFFINGTON'S INCCompressed Tablets Phenobarbital 16 mg, 32 mg and
0.1 Gm

ELINT, LATON & COMPANY

Tablets Phenobarbital (White and Green) 16 mg 32 mg and 01 Gm

GANE AND INGRAM, INC

Phenobarbital (*Powder*) bulk

MENCK & Co, INC

Phenobarbital (*Powder*) bulk

THE WM S MERRILL COMPANY

Tablets Phenobarbital 16 mg 32.5 mg 01 Gm

SMITH DORSEY COMPANY

Tablets Phenobarbital 8 mg, 16 mg 32.5 mg and 01 Gm

THE URJOHN COMPANY

Tablets Phenobarbital 16 mg 32.5 mg 01 Gm Supplied in both white and green tablets

WILLIAM R WARNER & Co, INC

Tablets Phenobarbital 16 mg 32 mg and 01 Gm

WARREN-TECO PRODUCTS COMPANY

Tablets Phenobarbital 16 mg 32.5 mg 01 Gm

WINTHROP CHEMICAL COMPANY, INC

Luminal (*Powder*) bulk

Elixir Luminal Each 4 cc contains 162 mg in a menstruum containing alcohol 26 per cent

Tablets Luminal 162 mg 324 mg and 109 mg

U S patent 1 075 872 (May 7 1912 expired) U S trademark 87 327

PHENOBARBITAL SODIUM—Soluble Phenobarbital, Soluble Phenobarbitone—U S P—Luminal Sodium—Contains not less than 89 per cent and not more than 91.5 per cent of phenobarbital ($C_{12}H_{12}N_2O_3$) calculated on a moisture free basis the moisture being determined on a separate portion by drying at 140° C for 6 hours U S P

For description and standards see the U S Pharmacopeia under Phenobarbital Sodium and Phenobarbital Sodium Tablets

Actions and Uses—The same as those of phenobarbital except that it may be injected

Dosage—For hypodermic injection phenobarbital sodium is used in the form of 20 per cent solution prepared by dissolving the salt in boiled and cooled distilled water, 2 cc of the solution contains 0.4 Gm of phenobarbital sodium.

Phenobarbital sodium may be given hypodermically in doses of 0.1 to 0.3 Gm.

Caution Aqueous solutions of phenobarbital sodium are not stable but decompose on standing, on boiling a precipitation occurs.

ABBOTT LABORATORIES

Phenobarbital Sodium (*Powder*) bulk

Phenobarbital Sodium (*Powder*) 0.13 Gm ampuls

Tablets Phenobarbital Sodium 65 mg (hypodermic) and 0.1 Gm

ENDO PRODUCTS, INC

Sodium Phenobarbital Solution in Propylene Glycol
0.16 Gm in 2 cc ampuls and 0.325 Gm in 2 cc ampuls

GANE AND INGRAM, INC

Phenobarbital Sodium (*Powder*) 30 cc 60 cc and 120 cc bottles

Tablets Phenobarbital Sodium 109 mg

LAKEVIEW LABORATORIES, INC

Phenobarbital Sodium (*Powder*) 0.13 Gm ampuls

Solution Phenobarbital Sodium and Benzyl Alcohol
1 cc and 2 cc ampuls Each cubic centimeter contains 0.162 Gm of phenobarbital sodium and 20 mg of benzyl alcohol dissolved in propylene glycol

MALLINCKRODT CHEMICAL WORKS

Phenobarbital Sodium (*Powder*) bulk

MERCK & Co., INC

Phenobarbital Sodium (*Powder*) bulk

WINTHROP CHEMICAL COMPANY, INC

Luminal Sodium (*Powder*) bulk

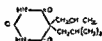
U S patent 1 025 872 (May 7 1912 expired) U S trademark
87 327

Luminal Sodium Solution in Propylene Glycol: 2 cc. ampuls. Each cubic centimeter contains luminal sodium 0.16 Gm, dissolved in propylene glycol. The solution may be administered intramuscularly or subcutaneously, but not intravenously.

Luminal-Sodium (Powder): 130 mg and 324 mg ampuls

Tablets Luminal-Sodium: 162 mg, 324 mg and 109 mg and 648 mg (hypodermic).

SANDOPTAL,—5-Isobutyl-5-allyl barbituric acid—5-Isobutyl-5-allyl malonylurea— $C_{13}H_{18}O_4N_2$,—M W 224.25



Actions and Uses—The same as those of barbital and its therapeutically useful derivatives.

Dosage—For mild insomnia, 0.2 Gm, for use in obstinate cases of insomnia, 0.4 to 0.8 Gm.

Tests and Standards—

Sandoptal occurs as a white, crystalline, odorless powder, with a slightly bitter taste, completely soluble in ethyl alcohol, acetone, chloroform ether, ethyl acetate and glacial acetic acid slightly soluble in cold water, sparingly soluble in boiling water and petroleum ether insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 138-139°C. It is stable in air.

[illegible]

acid and 1 cc of barium nitrate solution (*sulfate*), no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Incinerate about 1 Gm of sandopal, accurately weighed the residue does not exceed 0.1 per cent Dissolve about 0.5 Gm of sandopal, accurately weighed in 25 cc of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth normal sodium hydroxide solution, using thymolphthalein as an indicator—the amount

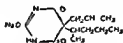
of tenth normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of isobutyl allyl barbituric acid

SANDOZ CHEMICAL WORKS, INC

Tablets Sandoptal 02 Gm

U S trademark applied for

SECONAL SODIUM.—Sodium 5 allyl-5-(1 methylbutyl) barbiturate— $C_{17}H_{19}O_3N_2Na$ —M W 260.27



Actions and Uses.—The actions and uses of seconal sodium are essentially those of barbital but it is described as a short-acting barbiturate. It is more active than barbital and is used in correspondingly smaller doses.

Dosage.—The average adult dose is from 0.1 to 0.2 Gm. When oral administration is contraindicated, seconal sodium may be administered rectally. Smaller doses of seconal sodium are sedative, larger doses are hypnotic. For use in obstetrics and as a preanesthetic sedative the following dosage has been suggested. In obstetrics, an initial dose of 0.3 Gm followed by 0.7 Gm to 0.2 Gm doses at appropriate intervals up to a total of no more than 1.2 Gm within a twelve hour period, as a preanesthetic agent, 0.2 Gm to 0.3 Gm one half to one hour before the patient is sent to the operating room.

Tests and Standards—

Seconal sodium occurs as a white hygroscopic, odorless powder possessing a bitter taste, very soluble in water, soluble in alcohol and practically insoluble in ether. An aqueous solution of seconal sodium is alkaline to litmus.

Dissolve about 1 Gm of seconal sodium in 100 cc of distilled water in a 500 cc beaker and add sufficient 1 per cent acetic acid to make the solution distinctly acid to litmus. Stir vigorously for a few minutes and add an additional 150 cc of distilled water. Heat to boiling and boil until the precipitate dissolves and no oily particles float on the surface of the liquid. Allow the solution to stand overnight at room temperature. Collect the resultant crystals of allyl (1 methyl butyl) barbituric acid on a porous plate and dry at room temperature; the crystals melt between 96 and 100 C. Dissolve 0.3 Gm of seconal sodium in 10 cc of distilled water and divide the solution into two portions; to one portion add 1 cc of mercuric chloride solution, a white precipitate results, soluble in excess of ammonia water; to the other portion add 5 cc of silver nitrate solution, a white precipitate results, soluble in excess of ammonia water. Transfer about 0.5 Gm of seconal sodium to a 50 cc beaker and boil with 5 cc of a 25 per cent solution of sodium hydroxide; the product decomposes and ammonia is evolved. Dissolve about 0.5 Gm

of secional sodium in 50 cc of distilled water, add 5 cc of diluted nitric acid and filter through paper separate 10 cc portions of the filtrate yield no turbidity on the addition of 1 cc of barium chloride solution (sulfate) and no more opalescence on the addition of 1 cc

potassium permanganate the purple color is discharged and a brown precipitate is formed Dry about 1 Gm accurately weighed of secional sodium to constant weight at 90 C the loss in weight does not exceed 1 per cent

Transfer about 1 Gm accurately weighed, of secional sodium to a 250 cc separatory funnel add 50 cc of distilled water and 10 cc of diluted hydrochloric acid and extract the mixture with eight successive 25 cc portions of ether Filter the ethereal extracts evaporate to dryness on the steam bath and dry to constant weight at 90 C the allyl (1 methyl butyl) barbituric acid obtained is not less than 90.5 nor more than 92 per cent calculated to the dried substance Evaporate the aqueous residue to dryness on the steam bath transfer to a tared platinum dish and add 5 cc sulfuric acid cautiously evaporate the excess acid and ignite to constant weight at 900 C the weight of sodium sulfate calculated as sodium is not more than 9.4 nor less than 8.7 per cent calculated to the dried substance

Transfer an accurately weighed sample of about 10 mg to a micro Kjeldahl flask and digest with 2 cc of sulfuric acid and 0.01 Gm of selenium Dilute the clear solution to 10 cc, make alkaline with 30 per cent sodium hydroxide and distil the ammonia into 10 cc of one hundredth normal alkali using methyl red as indicator the nitrogen content is not more than 10.85 nor less than 10.70 per cent calculated to the dried substance

ELI LILLY AND COMPANY

Secional Sodium (Powder) bulk

Pulvules Secional Sodium 50 mg and 0.1 Gm

Suppositories Secional Sodium 0.13 Gm

U. S. patent 1,954,429 (April 10, 1934 expires 1951) U. S. trade mark 328,662

VINBARBITAL SODIUM—*Delvinal Sodium*—Sodium 5 ethyl 5 (1 methyl 1 butenyl) barbiturate

Actions and Uses—The actions and uses of vinbarbital sodium are somewhat similar to those of a barbituric acid derivative having a short induction period and a moderate duration of action. Indications for its use are claimed to include general sedation and hypnosis, preoperative sedation, preanesthetic hypnosis, obstetrical sedation and amnesia. While this substance is claimed to have a relatively low incidence of side effects, published reports indicate that it is not unlike other barbiturates in that it occasionally may cause side effects such as epigastric discomfort, nausea, dizziness, pallor and even fall in blood pressure.

Dosage—As a sedative, 32 mg repeated three to four times daily, as a sedative and hypnotic, 0.1 Gm to 0.2 Gm, as a preoperative hypnotic, 0.1 Gm to 0.2 Gm, in psychiatric cases, 0.1 Gm to 0.4 Gm, for obstetric sedation and amnesia, 0.2 Gm to 0.4 Gm, with or without scopolamine. Children must be given correspondingly smaller doses.

Caution—Unbuffered aqueous solutions of vinbarbital sodium are not stable. The powder is hygroscopic, and if capsules are broken or exposed to high humidity the contents are affected by both moisture and carbon dioxide.

Vinbarbital sodium occurs as a white, odorless powder, possessing a bitter taste, soluble in alcohol and water, slightly soluble in ether and chloroform. A 1 per cent aqueous solution is alkaline to phenolphthalein and has a pH between 8.5 and 9.5.

Tests and Standards—

To 5 cc of a 10 per cent solution of vinbarbital sodium slowly add 2 cc of dilute hydrochloric acid, allow the precipitate to crystallize, filter, wash and dry at 90°C. the melting point of the vinbarbital is 161 to 163°C.

Transfer 5 cc portions of a 10 per cent solution of vinbarbital sodium to two test tubes and to one add 1 cc of mercury bichloride solution, a white precipitate results soluble in 10 cc of ammonium hydroxide; to the other portion add 5 cc of silver nitrate solution, a white precipitate results soluble in 5 cc of ammonium hydroxide.

Dissolve 0.1 Gm of vinbarbital sodium in 10 cc of distilled water, add 1 cc of sodium hydroxide solution and 4 drops of potassium permanganate solution, a green color develops in twenty seconds; add 5 cc of dilute hydrochloric acid, the solution turns pink and a brown precipitate appears. Boil 0.5 Gm of vinbarbital sodium with 5 cc of 25 per cent sodium hydroxide, ammonia is evolved.

Acidify 40 cc of a 10 per cent solution of vinbarbital sodium with dilute nitric acid and filter, separate portions of 20 cc each of the filtrate yield no opalescence with 1 cc of silver nitrate solution (chloride), no turbidity with 1 cc of barium nitrate solution (sulfate), no coloration or precipitation on saturation with hydrogen sulfide (salts of heavy metals).

Transfer about 3 Gm of vinbarbital sodium accurately weighed to a glass stoppered flask, add 50 cc of anhydrous ether and shake for ten minutes. Decant the supernatant liquid through a filter and again extract the residue with 15 and 10 cc portions of ether. Evaporate the combined filtered extracts to dryness in a tared beaker on the steam bath, the residue does not exceed 0.5 per cent.

Transfer about 0.5 Gm of vinbarbital sodium accurately weighed to a separator, add 30 cc of water and 10 cc of dilute hydrochloric acid. Extract with seven successive portions of ether, filter the com-

Hydantoin Derivatives

DIUM — U S P —
When dried for 4 hours
per cent and not more
(C₁₂H₁₂N₂O₂) U S P



For description and standards see the U S Pharmacopeia under Diphenylhydantoin Sodium and Diphenylhydantoin Sodium Capsules

Actions and Uses—Diphenylhydantoin sodium is an anticonvulsant with a relatively weak hypnotic action. It is used in the treatment of epileptic patients who are not benefited by phenobarbital or bromides and those in whom these drugs induce disagreeable side actions. Diphenylhydantoin sodium appears to be more effective in controlling seizures of the grand mal type than in those of the petit mal. It does not cure congenital

is strongly alkaline and it may give rise to gastric irritation

Dosage—The optimum dosage of diphenylhydantoin sodium must be determined by the daily observation of its effects by the physician. The influence of the drug on seizures and the appearance of any of the side actions enumerated must be a guide to the dosage. Mild symptoms do not necessarily require that the dosage be stopped. The beginning adult dose is 0.1 Gm (1½ grains) with at least half a glass of water three times daily. If necessary this dose may be increased gradually to 0.2 Gm

means. Children under 4 years of age may start with 0.03 Gm (one half grain) mixed with cream (to disguise the bitter taste and to prevent gastric irritation) twice a day. Obviously such

doses require the most careful supervision. If this dose is borne without side actions the dosage may be increased to 0.03 Gm (one half grain) three or four times a day. Every slight increase in dosage is made only after the physician is convinced that such increase is necessary and that no harm is to be anticipated.

The transition from phenobarbital, bromides or other hypnotic type drugs to diphenylhydantoin sodium should be made gradually with some overlapping in dosage. By this procedure the danger of phenobarbital or bromide withdrawal symptoms (increased number of seizures) is minimized and side actions incident to the beginning administration of diphenylhydantoin sodium are lessened.

PARKE, DAVIS & COMPANY

Kapseals Dilantin Sodium 0.1 Gm and 30 mg

U. S. trademark applied for

PREMO PHARMACEUTICAL LABORATORIES, INC

Capsules Diphenylhydantoin Sodium 30 mg and 0.1 Gm

CHAPTER XXIII

SERUMS AND VACCINES

Under this heading are described in the following pages agents of a complex biologic nature which are used in diagnosis, in prevention, and in the treatment of disease and which depend for their action on various phases and relations of immunity

Federal Regulations—The urgent need for control of many of these potent and, in some cases dangerous products has been partly met by a federal law entitled "An act to regulate the sale of viruses, serums, toxins, and analogous products in the District of Columbia, to regulate interstate traffic in said articles and for other purposes." Under this law the importation, exportation or interstate sale of these products is expressly forbidden unless the manufacturer holds a license issued on the recommendation of the U. S. Public Health Service.

It is to be noted that the protection of the federal law is of avail only in the case of prophylactic and therapeutic preparations which are imported or shipped for exportation or interstate sale. Only products which are licensed under the law referred to and which have not been found to conflict with the rules of the Council will be found listed here. In purchasing the products for use, preference should be given to those which have been kept continually at a low temperature.

Dating of Biologic Products—The federal law requires that each product shall have an expiration date which shall not be expected to give a satisfactory result. The following table prescribes

for each class of product how long after date of manufacture or issue this expiration date may be, but the temperature at which the product is kept after leaving the manufacturer's hands cannot be controlled. Physicians would do well to secure their biologic products from stocks which are shown by actual continuous thermometer records to have been kept in cold storage. This is particularly applicable to the more rapidly deteriorating products, such as smallpox vaccine and the various immune serums.

Official potency standards have been established and official potency tests are made at the National Institute of Health prior to the release of each lot, for the following products: botulinus antitoxin, diphtheria antitoxin, Cl. histolyticum antitoxin, Cl. histolyticum antitoxin mixture, anti-serum, anti-phthiria

toxin for the Schick test and scarlet fever streptococcus toxin for the Dick test and for immunization. For these products the dating of each lot is based on the last test for potency, that is, the date of manufacture is taken as the last date of satisfactorily passing a potency test. For all other biologic products, the testing for potency is on a less satisfactory basis, and the date of manufacture is counted as the date of removal from the animal in case of animal products, or the date of cessation of growth in the case of other products. For the purpose of determining the expiration date, the date of issue may be used instead of the date of manufacture, provided the product has been kept between the date of manufacture and the date of issue not longer than the following periods at the corresponding temperature: twenty four months constantly below 0 C, or twelve months constantly below 5 C, or six months constantly below 10 C, or three months constantly below 15 C.

Added Preservatives—The safeguarding of serums, vaccines, etc., against bacterial contamination usually requires the addition of some antiseptic. The most commonly used antiseptics are cresol (0.4 per cent), phenol (0.5 per cent), glycerin, and organic mercury compounds.

Untoward Effects—The use of serums and serum preparations is sometimes followed by certain untoward manifestations. These are due usually to sensitivity of the individual to animal products, especially horse serum, and in certain cases may be avoided by the use of serums which have been altered by the action of enzymes or by using serums from the bovine species or from sheep or goats. Serums and antitoxins unless made by the inoculation of the horse, must show on the label the species of animal used.

The following outline sets forth the classification of the preparations as described in this chapter.

SERUMS

NORMAL SERUMS OR NORMAL BLOOD DERIVATIVES

- Citrated normal human plasma
- Human immune globulin
- Normal human serum

IMMUNE SERUMS

Antitoxic serums

Antitoxins

- Antivenin (*Crotalus*)
- Botulism antitoxin
- Diphtheria antitoxin
- Diphtheria antitoxin, Bovine
- Diphtheria antitoxin, globulin modified
- Gas gangrene antitoxin (*Cl perfringens* and *Cl septicum*)

Gas gangrene antitoxin (*Cl perfringens Cl septicum*
Cl novyi Cl sordellii and Cl histolyticum)
 Tetanus gas gangrene antitoxin (*Cl tetani Cl sep-*
ticum and Cl tetani)
 Scarlet fever streptococcus antitoxin
 Staphylococcus antitoxin
 Tetanus antitoxin
 Tetanus antitoxin Bovine

Antibacterial serums

Antianthrax serum
 Antidysenteric serum
 Antierysipeloid serum
 Antimeningococcic serum
 Antipneumococcic serums
 Antipneumococcic horse serum Type 1 2 1 and 2
 combined
 Antipneumococcic rabbit serum Types 1 2 3 4 5 6
 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
 22 23 24 25 27 28 29 31 32

NATURALLY PRODUCED ANTIBODIES

Human measles immune serum
 Human scarlet fever immune serum

VACCINES

Active immunization General considerations

ATTENUATED LIVING VIRUSES OR KILLED VIRUSES

Rabies vaccine
 Rabies vaccine (Cumming)
 Rabies vaccine (Harris)
 Rabies vaccine (Pasteur)
 Rabies vaccine (Semple)
 Rabies vaccine (Semple) chloroform killed

BACTERIAL TOXINS

Scarlet fever streptococcus toxin

BACTERIAL TOXINS MODIFIED

Staphylococcus toxoid
 Tetanus toxoid
 Tetanus toxoid alum precipitated refined
 Tetanus toxoid alum precipitated refined

BACTERIAL VACCINES

- Bacterial vaccine made from the acne bacillus
- Bacterial vaccine made from *Brucella melitensis abortus* or suis (Undulant Fever vaccine)
- Bacterial vaccine made from the cholera vibrio
- Bacterial vaccine made from the plague bacillus
- Bacterial vaccine made from staphylococci
- Bacterial vaccine made from the typhoid bacillus
- Bacterial vaccine made from the typhoid bacillus and the paratyphoid A and B bacilli

DIAGNOSTIC AGENTS

- Diphtheria toxin for Schick test
- Scarlet fever streptococcus toxin for Dick test
- Scarlet fever streptococcus antitoxin for Schultz Charlton test
- Trichinella extract
- Tuberculin
 - Purified protein derivative of tuberculin
 - Old tuberculin
 - New tuberculin P F
 - New tuberculin B I dried
 - New tuberculin F R
 - New tuberculin T R dried
 - Tuberculin Denys

SERUMS

Normal Serums or Normal Blood Derivatives

This section lists those preparations derived from normal blood such as plasma serum or globulins. Any antibodies which the preparations may contain have been produced naturally in the body. There is some evidence that human serum preparations may by carrying a virus be instrumental in leading to the development of a form of infectious jaundice. They may also lead to reactions of the type usually regarded as allergic.

HUMAN IMMUNE GLOBULIN—Measles Prophylactic—Placental Extract—A sterile solution of antibodies obtained from the placentae expelled by healthy women (*Homo sapiens*). Each preparation shall be composed of a pool from at least ten individuals. Human immune globulin complies with the requirements of the National Institute of Health of the United States Public Health Service U S P.

For description and standards see the U S Pharmacopeia under Human Immune Globulin.

Actions and Uses—Human immune globulin is useful in the prevention and modification of measles. It is equivalent in usefulness to convalescent serum but has the advantage of universal

PARKE, DAVIS & COMPANY

Immune Globulin (Human) 2 cc and 10 cc vials Preserved with 0.1 per cent of merthiolate

SHARP & DOHME, INC

Immune Globulin (Human) 2 cc and 10 cc ampul vials Preserved with 0.5 per cent of phenol

E. R. SQUIBB & SONS

Immune Globulin (Human) 2 cc and 10 cc vials Preserved with merthiolate 1:10,000 and 0.2 per cent of phenol

WYETH, INCORPORATED

Immune Globulin (Human) 2 cc and 10 cc vials Preserved with 0.1 per cent of phenol and 0.01 per cent of merthiolate

CITRATED NORMAL HUMAN PLASMA—Normal Human Plasma—Citrated Normal Human Plasma is the sterile plasma obtained by pooling approximately equal amounts of the liquid portion of citrated whole blood from eight or more humans (*Homo sapiens*) who have been certified by a qualified doctor of medicine as free from any disease which is transmissible by blood transfusion at the time of drawing the blood. Each bleeding is drawn under aseptic precautions into individual sterile centrifuge bottles already containing 50 cc of a sterile, 4 per cent solution of sodium citrate in isotonic solution of sodium chloride for each 500 cc of whole blood. The cell free plasma is separated by centrifugation and transferred to a pool by means of a closed system. Sterility tests are made, a preservative is added and the plasma is distributed into final containers through a closed system. Citrated normal human plasma complies with the requirements of the National Institute of Health of the United States Public Health Service.

Citrated normal human plasma may be dispensed as liquid plasma, as frozen plasma or as dried plasma. Citrated normal human plasma must be free from harmful substances detectable by animal inoculation and must not contain an excessive amount of preservative." U. S. P.

For description and standards see the U. S. Pharmacopeia under Citrated Normal Human Plasma.

Actions and Uses—Citrated normal human plasma is administered in the treatment of surgical and traumatic shock, in the treatment of burns when loss of available plasma occurs to combat hypoproteinemia and as a temporary substitute for whole blood in the treatment of hemorrhage when whole blood is not immediately available. Plasma and serum may be considered satisfactory substitutes for whole blood except in those cases in which the administration of red blood corpuscles is regarded as essential.

2 198 752 (April 30 1940 expires 1957) 2 199 815 2 199 816 2 199 817
 (May 7 1940 expires 1957) 2 225 774 (Dec 24 1940 expires 1957)
 2 340 102 (Jan 25 1944 expires 1961) U S trademarks 357 071 and
 380 366

Lyovac Normal Human Plasma 500 cc vacule ampul
 vial containing a sufficient amount (preserved with phenyl
 mercuric borate 1 25 000) to yield 500 cc of restored plasma
 packaged with a 500 cc bottle of distilled water as a diluent
 (containing 0.1 per cent citric acid and equipment for intra
 venous injection)

NORMAL HUMAN SERUM—Human Serum—Nor
 mal Human Serum is the sterile serum obtained by pooling
 approximately equal amounts of the liquid portion of coagulated
 whole blood from eight or more humans (*Homo sapiens*) who
 have been certified by a qualified doctor of medicine as free from
 any disease which is transmissible by blood transfusion at the
 time of drawing the blood. Each bleeding is drawn under
 aseptic precautions into individual sterile centrifuge bottles and
 allowed to coagulate for at least 12 hours and not more than
 24 hours. The cell free serum is separated by centrifugation
 and transferred to a pool by means of a closed system. Steril
 ity tests are made a preservative is added the serum is passed
 through a bacteria excluding filter and finally distributed into
 the final containers through a closed system. Normal Human
 Serum complies with the requirements of the National Institute
 of Health of the United States Public Health Service U S P

For description and standards see the U S Pharmacopeia
 under Normal Human Serum

Action Uses and Dosage—See Citrated normal human
 plasma

CUTTEN LABORATORIES

Normal Human Serum 50 cc and 250 cc bottles 1 10 000
 sodium ethylmercuri thiosalicylate is used as a preservative

SAMUEL DEUTSCH SERUM CENTER MICHAEL REESE HOS PITAI

Normal Human Serum 250 cc bottle Phenylmercuric
 borate 1 15 000 is used as a preservative

Normal Human Serum (Diluted) 250 cc bottle Diluted
 with 250 cc of isotonic solution of sodium chloride Phenyl
 mercuric borate 1 15 000 is used as a preservative

HYLAND LABORATORIES

Normal Human Serum 250 cc bottle Preserved with
 1 15 000 phenylmercuric borate

Immune Serums for Prophylactic or Therapeutic Purposes

ANTITOXIC SERUMS

Antibodies are usually directed against the toxins or other soluble products of bacteria or against the bacteria themselves. All the antibodies enumerated below are formed in the blood serum of the larger domestic animals by active immunization, that is, by injecting the animal with an antigen. The animal is then bled to furnish the serum which afterward may be purified, in the case of the antitoxins and some other immune serums, to remove as many inactive substances as possible leaving the antibody in a concentrated form.

ANTITOXINS

The antitoxins are among the most useful of the antibodies. As the name implies they antagonize toxins. Though toxins may be secreted by plants other than the bacteria and by some animals, e. g., the snake, the typical toxins are the soluble poisons produced by diphtheria and tetanus bacilli.

Diphtheria and tetanus are dangerous diseases almost entirely on account of the action of these toxins and conversely, their prevention or cure when the organisms have once gained entrance to the body depends on the work of the particular antitoxin. Though the presence of the toxin stimulates the body to produce antitoxin, this active immunity may not be enough to save life, and at any rate assistance by the injection of antitoxin ready made in the blood serum of another animal hastens the cure or may prevent the disease.

In some individuals eruptions occur after injection of antitoxin rarely swelling and pain in the joints. In others, more severe symptoms have been observed and in a few instances sudden death has occurred. These conditions are due not to the antitoxin but to the horse serum in which it is contained.

Some preparations of antitoxin globulin modified differ from U. S. P. antitoxins in that the refinement process includes a selective digestion of the proteins of the antitoxin horse plasma. As a result of this process up to 80 per cent coagulable protein is digested. The remaining portion of globulin associated with antitoxin becomes highly despeciated. Injections of globulin modified antitoxin are followed by far fewer instances of serum sickness than are injections of antitoxin contained in unaltered horse serum globulin.

Actions and Uses—Tests on animals show that the venom of certain snakes may be neutralized by the employment of a serum obtained from animals that have been injected with venom from a snake of the same family. *Crotalus antitoxin* is used to neutralize the venom injected by the bite inflicted by members of the *crotalus* family.

Dosage—The serum is administered intramuscularly or subcutaneously, in cases seen late or in the presence of severe symptoms it may be administered intravenously. Certain observations seem to show that there is great advantage in giving the serum in the vicinity of the bite. Use of the antitoxin never should be allowed to replace first aid measures especially local incisions and suction. Perhaps 50 cc of serum is as small an amount as is likely to prove beneficial.

ANTIVENIN (LATRODECTUS MACTANS)—An antitoxic serum prepared by immunizing horses against the venom of the black widow spider (*Latrodectus mactans*).

Actions and Uses—This material, which is standardized on the basis of its ability to neutralize the venom of the black widow spider when the two are injected simultaneously in mice is claimed to be indicated in the treatment of patients suffering from symptoms due to bites inflicted by the black widow spider (*Latrodectus mactans*). Prior to use, tests for serum sensitivity should be made. Test material consisting of 1:10 dilution of isotonic solution of normal equine serum which is injected intradermally. If there is a positive skin reaction in eye test consisting of placing a few drops of the test material on the conjunctiva and watching for ten minutes should be undertaken. If there is a negative result from the skin test the therapeutic serum can be administered. However if there is a positive reaction in the eye following the positive skin test serum therapy should be avoided. If there is a positive skin test and a negative eye test, the individual may be desensitized before administering the serum. The amount of material injected into the skin for the intradermal test should be not more than 0.02 cc of the test material. The result can be evaluated in ten minutes a positive reaction consisting of an urticarial wheal surrounded by a zone of erythema.

Associated treatment includes hot plunge baths intravenous injection of magnesium sulfate, 20 cc of 10 per cent solution or intravenous injection of 10 per cent calcium gluconate. Barbiturates may be used for restlessness. Apparently nothing is gained by local treatment at the site of the bite.

Dosage—An injection of 25 cc of serum is administered intramuscularly.

BOTULISM ANTITOXIN—An antitoxic serum prepared by immunizing animals against two types of the toxin of *Clostridium botulinum*.

Actions and Uses—For prophylaxis and treatment of botulism. The clinical value of the antitoxin is uncertain.

Dosage—Prophylactic: subcutaneous injections of not less than 2,500 units of bivalent antitoxin. Therapeutic: intravenous injection of not less than 10,000 units of the bivalent antitoxin to be repeated as indicated by the nature of the case.

JENSEN SALSBERG LABORATORIES, INC.

Botulism Antitoxin Vial containing 2,500 units each of type A and type B botulism antitoxin. Preserved with phenol 0.5 per cent, glycerin 0.5 per cent and sodium citrate 1 per cent.

LIEBERER LABORATORIES, INC.

Botulism Antitoxin Bivalent Globulin Modified Vial containing 10,000 units each of type A and type B botulism antitoxin. Preserved with phenol 0.4 per cent and 1:25,000 phenylmercuric borate.

DIPHTHERIA ANTITOXIN—Purified Antidiphtheric Serum.—Concentrated Diphtheria Antitoxin.—Antidiphtheric Globulins.—Diphtheria Antitoxin is a sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against diphtheria toxin. After the serum or plasma from the immunized animal has been collected the antitoxin bearing globulins are separated from the other constituents of the serum or plasma and dissolved in freshly distilled water. Sodium chloride and a preservative are then added and the solution is filtered through a bacteria excluding filter. Diphtheria Antitoxin has a potency of not less than 500 antitoxic units per cc. It complies with the requirements of the National Institute of Health of the United States Public Health Service. *U. S. P.*

For description and standards see the U. S. Pharmacopœia under Diphtheria Antitoxin.

Actions and Uses—For prophylaxis and treatment of diphtheria.

Dosage—By parenteral injection: therapeutic, 20,000 units; prophylactic, 1,000 units.

LIEBERER LABORATORIES, INC.

Diphtheria Antitoxin, Globulin Modified Vials containing 5,000, 10,000 and 20,000 units.

PITMAN MOORE COMPANY

Diphtheria Antitoxin Pepsin Digestion Refined Syringes containing 1,000 and 10,000 units and vials containing 20,000 units. Preserved with merthiolate 1:10,000.

GAS GANGRENE ANTITOXIN antitoxic serum prepared by *Cl perfringens* (Welch) and *Cl septicum* after the desired degree of potency is obtained the horses are bled the fluid portion of the blood separated from the cellular elements and the serum prepared in a manner similar to that used for other antitoxic serums Potency is determined according to the methods described by the National Institute of Health

Actions and Uses—Used in prevention and treatment of gas gangrene The clinical value of this antitoxin is questionable

Dosage—Therapeutic 10 000 to 40 000 units each of *Cl perfringens* and *Cl septicum* intramuscularly or intravenously preferably the latter, repeated every twelve to twenty four hours depending on the symptoms in the individual case

CUTLER LABORATORIES

Gas Gangrene Antitoxin Bottle containing 10 000 units each of *Cl perfringens* and *Cl septicum* antitoxins Preserved with 0.35 per cent tricresol

ELI LILLY AND COMPANY

Gas Gangrene Antitoxin Concentrated (Combined) Vial containing 10 000 each of *Cl perfringens* and *Cl septicum* antitoxins

GAS GANGRENE ANTITOXIN (POLYVALENT)

—A polyvalent antitoxin the toxins of *Cl perfr* and optionally those of *Cl histolyticum* The toxins are individually prepared by growing respective organisms anaerobically in suitable broth mediums Some horses are immunized with injections of but one toxin while others are immunized against several simultaneously When a potent antitoxic serum (as indicated by potency tests applied to trial bleedings) is obtained aseptic bleedings of plasma are made

Actions and Uses—Used in prevention and treatment of gas gangrene The clinical value of this antitoxin is questionable

Dosage—The minimum therapeutic dose is 10 000 units each of *Cl perfringens* and *Cl septicum* antitoxins and optionally 1 500 units each of *Cl novyi* and *Cl sordellii* antitoxins and 3 000 units of *Cl histolyticum* antitoxin intravenously From one to four times this dose may be given initially and supplemented by additional injections in one to four hours or longer as indicated by the symptoms

LEDERLE LABORATORIES INC

Gas Gangrene Antitoxin Globulin Modified (Polyvalent) Vial containing 10 000 units each of *Cl perfringens* and *Vibrio septique* antitoxins 1 500 units each of *Cl novyi*

and *sordelli* antitoxins, and 300 units of *Cl histolyticum* antitoxin. Preserved with 0.4 per cent phenol and 1:20,000 phenyl mercuric borate.

NATIONAL DRUG COMPANY

Gas Gangrene Antitoxin Refined and Concentrated Globulin (Trivalent): Syringe or vial containing 10,000 units each of *Cl perfringens* and *Cl septicum* antitoxins and 1,500 units of *Cl oedematis* (Aer. vi.) antitoxin. Preserved with 0.4 per cent tricesal.

PARKE, DAVIS & COMPANY

Gas Gangrene Antitoxin Refined and Concentrated (Combined, Trivalent): Vial containing 10,000 units each of *Cl perfringens* and *Cl septicum* antitoxins and 1,500 units of *Cl nozys* antitoxin. Preserved with 0.5 per cent phenol.

L. R. SQUINN & SONS

Gas Gangrene Antitoxin: Vial containing 10,000 units each of *Cl perfringens* and *Cl septicum* antitoxins and 1,500 units of *Cl nozys* antitoxin. Preserved with 1:20,000 merthiolate and 0.25 per cent of phenol.

WARTH, INCORPORATION

Gas Gangrene Antitoxin, Concentrated and Refined (Tri-Valent): Syringe and vial each containing 10,000 units each of *Cl perfringens* and *Cl septicum* antitoxins and 1,500 units of *Cl nozys* antitoxin. Preserved with 0.25 per cent phenol and 0.005 per cent merthiolate.

TETANUS
antitoxic
vidually,
ticum (V)

After the
bled, the fluid portion of the blood separated from the cellular elements, and the serum prepared in a manner similar to that used for other antitoxic serums. Unitage of the tetanus antitoxin, *perfringens* antitoxin, and *vibrio septique* antitoxin is determined according to the method prescribed by the National Institute of Health.

Actions and Uses—Used in prevention of gas gangrene. The clinical value of this antitoxin is questionable except as relates to the tetanus antitoxin present.

Dosage—Prophylactic: 1,500 units of tetanus antitoxin and 2,000 units each of *Cl perfringens* and *Cl septicum* antitoxins by parenteral injection. This dose may be repeated at intervals of from five to seven days depending on the severity of the wound. Local infiltration of the wound may be advisable.

CUTTEN LABORATORIES

Tetanus Gas Gangrene Antitoxin Syringe and vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl perfringens* and *Cl septicum* antitoxins Preserved with 0.35 per cent tricresol

LEDERLE LABORATORIES, INC

Tetanus-Gas Gangrene Antitoxin, Globulin Modified Vials containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl perfringens* and *Cl septicum* antitoxins Preserved with 0.35 per cent phenol and 1:20,000 phenylmercuric acetate

ELI LILLY AND COMPANY

Tetanus Gas Gangrene Antitoxin (Combined) Vial containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl perfringens* and *Cl septicum* antitoxins

NATIONAL DRUG COMPANY

Tetanus Gas Gangrene Antitoxin (Monovalent), Refined and Concentrated Globulin Syringe and vial each containing 1,500 units of tetanus antitoxin and 4,000 units of *Cl perfringens* antitoxins Preserved with 0.4 per cent tricresol

Tetanus-Gas Gangrene Antitoxin (Trivalent) Refined and Concentrated Globulin Syringe and vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl perfringens* and *Cl septicum* antitoxins and 300 units of *Cl oedematis (Novyi)* antitoxin Preserved with 0.4 per cent tricresol

PARKE DAVIS & COMPANY

Tetanus-Gas Gangrene Antitoxin, Refined and Concentrated (Combined) Vials containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl perfringens* and *Cl septicum* antitoxins Preserved with 0.5 per cent phenol

PITMAN MOORE COMPANY

Tetanus Gas Gangrene Antitoxin (Combined) Pepsin Digestion Refined Syringe or vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Clostridium perfringens* and *Clostridium septicum* antitoxins

SHARP & DOHME, INC

Tetanus Gas Gangrene Antitoxin Mixed Syringe and ampul vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl perfringens* and *Cl septicum* antitoxins Preserved with 0.5 per cent phenol

I. R. SQUINN & SONS

Tetanus Gas Gangrene Antitoxin Vial containing 1 500 units of tetanus antitoxin and 2 000 units each of *C. perfringens* and *C. septicum* antitoxins. Preserve with 1 20 000 merthiolate and 0.25 per cent of phenol

U. S. STANDARD PRODUCTS CO.

Tetanus Gas Gangrene Antitoxin, Refined and Concentrated Syringe containing 1 500 units of tetanus antitoxin and 2 000 units each of *C. perfringens* and *C. septicum* antitoxins. Preserved with 0.4 per cent of cresol

WALTH INCORPORATED

Tetanus Gas Gangrene Antitoxin, Concentrated and Refined Syringe and vial each containing 1 500 units of tetanus antitoxin and 2 000 units each of *C. perfringens* and *C. septicum* antitoxins and package with a 1 cc. vial of dilute (1:10) antitoxin for determination of sensitivity to horse protein. Preserve with 0.25 per cent phenol and 0.005 per cent merthiolate

SCARLET FEVER STREPTOCOCCUS ANTITOXIN—Scarlet Fever Antitoxin—Refined Scarlet Fever Antitoxin—Anti Scarlet Fever Globulins—"Scarlet Fever Streptococcus Antitoxin is a sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against the toxin produced by the streptococcus regarded as causative of scarlet fever. Scarlet Fever Streptococcus Antitoxin has a potency of not less than 400 antitoxic units per cc. It complies with the requirements of the National Institute of Health of the United States Public Health Service. U. S. P.

For description and standards see the U. S. Pharmacopeia under Scarlet Fever Streptococcus Antitoxin

Actions and Uses—There is satisfactory evidence that scarlet fever is caused by hemolytic streptococci and that the administration of a serum containing the antitoxin produced by these organisms favorably influences the course of scarlet fever. It is also believed that temporary immunity against scarlet fever may be established through the use of such a serum, but the prophylactic use generally is not considered advisable. The serum is also used to distinguish the rash of scarlet fever from other rashes by the production of a blanched area at the site of its intradermal injection

Dosage—Prophylactic 3 000 U. S. P. H. S. units therapeutic 9 000 U. S. P. H. S. units

NATIONAL DRUG COMPANY

Scarlet Fever Streptococcus Antitoxin, Refined and Concentrated Syringes and vials containing 3 000 and 9 000 units respectively. Preserved with 0.4 per cent tricresol

PARKER, DAVIS & COMPANY

Scarlet Fever Streptococcus Antitoxin* Vials containing 3,000 and 9,000 units respectively

WYETH, INCORPORATED

Scarlet Fever Streptococcus Antitoxin (Refined and Concentrated): Syringes containing 3,000 and 9,000 units respectively

STAPHYLOCOCCUS ANTITOXIN.—Antitoxin prepared by immunizing horses with staphylococcus toxoid and/or staphylococcus toxin. The antitoxin is standardized on the basis of the international unit which was adopted by the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations in 1934, the unit being the equivalent to approximately 125 original antidermonecrotic units an antidermonecrotic unit being that amount of antitoxin required to neutralize one necrotizing dose of staphylococcus toxin.

Actions and Uses.—Staphylococcus antitoxin is suggested in the treatment of acute and severe staphylococcal infections with or without septicemia. Its use in treatment calls for adequate dosage administered early. Most of the antitoxin estimated to be necessary for the entire treatment of the infection should be injected during the first few hours after decision is made to use the serum. Supplementing the use of antitoxin in the more severe types of staphylococcal infections surgical drainage of accessible foci and transfusions with normal or immune donors should be a part of the treatment. Probably chemotherapeutic preparations should take precedence over this antitoxin in routine treatment.

Dosage.—For the treatment of localized infections 10,000 units. For the treatment of more severe infections from 30,000 to 100,000 units early during the first day in divided doses followed by from 20,000 to 100,000 units daily until the pulse rate and temperature have subsided and the blood cultures are sterile for three consecutive days.

TETANUS ANTITOXIN.—Purified Antitetanic Serum—Concentrated Tetanus Antitoxin—Refined Tetanus Antitoxin—Antitetanic Globulins—Tetanus Antitoxin is a sterile aqueous serum of immunized horses from the blood in bearing against the immunized globulins are separated from the other constituents of the serum or plasma and dissolved in freshly distilled water. Sodium chloride and a preservative are then added and the solution is filtered through a bacteria excluding filter. Tetanus antitoxin

has a potency of not less than 400 antitoxic units per cc. It complies with the requirements of the National Institute of Health of the United States Public Health Service U S P.

For description and standards see the U S Pharmacopeia under Tetanus Antitoxin.

Actions and Uses—Tetanus antitoxin is highly effective in the prevention of tetanus but its effectiveness when used in the treatment of the disease is much less certain.

Dosage—By parenteral injection therapeutic 20 000 units prophylactic 1 500 3 000 units. Intrathecal administration generally is regarded as inadvisable.

LEDERLE LABORATORIES, INC.

Tetanus Antitoxin Globulin Modified Vials containing 1 500 3 000 10 000 20 000 and 40 000 units respectively. The antitoxin differs from tetanus antitoxin U S P chiefly in the method of refinement which is based essentially on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin.

PITMAN MOORE COMPANY

Tetanus Antitoxin Pepsin Digestion Refined Vials containing 1 500 and 20 000 units respectively and syringes containing 1 500 units. The antitoxin differs from tetanus antitoxin U S P chiefly in the method of refinement which is based essentially on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin.

TETANUS ANTITOXIN BOVINE—An antitoxin complying with the standards for tetanus antitoxin U S P except that it is made from the serum of cattle instead of from the more generally used horse serum. It may be used in the treatment of individuals giving immunological evidence of or a history of sensitivity to horse serum.

Actions Uses and Dosage—Same as for Tetanus Antitoxin.

WYETH, INCORPORATED

Tetanus Antitoxin (Bovine) Vials containing 1 500 and 10 000 units respectively.

ANTIBACTERIAL SERUMS

More complex in action than the antitoxin and in general less satisfactory for therapeutic purposes are those antibodies which resist the bacteria themselves. They are believed to act primarily by combining chemically with antigens on the bacterial surfaces thereby rendering the bacteria susceptible to phagocytosis by polymorphonuclear and mononuclear leukocytes. The

sphere of usefulness of the antibacterial sera is open to much discussion and is in need of constant reevaluation in particular with the progress of chemotherapy with the sulfonamide drugs

ANTIANTHRAX SERUM—*Serum Antianthraxicum*.—A serum prepared by immunizing horses against virulent anthrax bacilli (*Bacillus anthracis*)

Actions and Uses—Good results have generally been reported from the use of the specific serum in human anthrax. Protective antibodies can be demonstrated experimentally

Dosage—Minimum of 50 cc intramuscularly or intravenously. Local subcutaneous injection is sometimes employed. The serum should be used as early as possible and used freely, the dose being repeated several times a day in severe cases

PARKE, DAVIS & COMPANY

Antianthrax Serum 50 cc syringe

ANTIDYSENTERIC SERUM—*Serum Antidysentericum*—The serum (polyvalent) of horses immunized against the Shiga bacillus (*Shigella dysenteriae*), its products of growth and other types of the dysentery bacilli. Probably chemotherapeutic preparations should take precedence over this antitoxin in routine treatment

Actions and Uses—A reduction in the mortality rate of bacillary dysentery through the use of some serums has been reported by some observers but not confirmed by all. It would seem that the best results may be ascribed to an antitoxic action in infections with the Shiga Kruse type of bacillus. Infections with the Flexner, Harris or Hiss Y strains which are relatively poor in toxin production have not been so favorably affected.

The serum is required to show a high agglutinin titer for the various types of dysentery bacilli

Dosage—From 20 to 100 cc subcutaneously or intramuscularly

ANTI-ERYSIPELOID SERUM—A serum containing the antibodies and antibacterial properties for *Erysipelothrix rhusiopathiae* (suus). The serum is prepared from horses subjected to increasing subcutaneous injections of live cultures of the organism. Potency is tested on pigeons in which 0.1 cc of the serum protects against infection lethal to controls in from three to four days

Actions and Uses—For treatment of the clinical condition known as erysipeloid which is not to be confused with erysipelas

Dosage—It is suggested that from 10 to 20 cc be administered subcutaneously or intramuscularly and quantities of 0.25 to 0.5 cc at numerous places about the border of the lesion.

PITMAN MOORE CO

Anti-Erysipeloid Serum (Refined) 10 cc vial Preserved with merthiolate 1:10,000

ANTIMENINGOCOCCIC SERUM
Antimeningococ-
tis Serum —
with cultures
(intracellularis)
in the require

of the National Institute of Health of the United States
Public Health Service U S P

For description and standards see the U S Pharmacopeia under Antimeningococcic Serum

The product may be concentrated in a manner similar to the concentration of diphtheria antitoxin

Actions and Uses—There is much doubt as to the value of antimeningococcic serum and it should not be used routinely. With the introduction of new chemotherapeutic agents the use of the serum has been supplemented or supplanted by these newer agents. Serologic (test tube) tests have been employed for determining the potency of antimeningococcic serum but there is no conclusive evidence that they measure the clinical usefulness of the product.

Dosage—Intravenous administration of this serum has generally replaced intrathecal use, dose intravenous, 50 cc for children and up to 100 cc for adults. When used intrathecally average dose for adults, 30 cc as early as possible in the disease repeated as indicated, for children doses up to 20 or 30 cc depending upon the amount of spinal fluid that can be withdrawn and the amount of serum that can be administered without untoward symptoms. The serum should be introduced slowly by gravity after the removal of a corresponding amount of spinal fluid. Administration should be controlled by blood pressure readings a drop of 10 mm of mercury during the administration being the signal for withdrawal of the needle. Intravenous route is especially indicated. In very early cases or in those cases accompanied by frank meningococcemia as demonstrated by positive blood cultures or by hemorrhagic rash but even in these a chemotherapeutic agent should be the first choice unless some absolute contraindication exists. Many experienced observers advise against intrathecal administration.

Naturally Produced Antibodies

In certain infectious diseases the etiological agent may be of such a nature as to make it impractical to produce a satisfactory immune serum in animals. In the absence of artificially

produced antibodies, the best source of antibodies is from human beings who are convalescing from the specific infectious disease. During convalescence from an active infection an individual's serum usually contains antibodies against the specific infectious agent far in excess of the amount normally present. The amount of antibodies, however, is not as great as when animals are artificially immunized by the repeated injection of antigens. An outstanding attribute of naturally produced antibodies or convalescent serums is that their source is from a member of the same species and thus there is less danger of a reaction to the protein of another species, but reaction may occur even with human serums. Even human serum, however, should be used only where there is definite need since infectious jaundice has been transmitted in this way.

HUMAN MEASLES IMMUNE SERUM — Measles Convalescent Serum — 'Human Measles Immune Serum is sterile serum obtained from the bloods of healthy individuals (*Homo sapiens*) who have recently recovered from an attack of measles. It complies with the requirements of the National Institute of Health of the United States Public Health Service.

U S P
For description and standards see the U S Pharmacopeia under Human Measles Immune Serum.

Actions and Uses — Human measles immune serum is administered during the incubation period to prevent or modify the expected attack of measles.

Dosage — To prevent the disease in infants and children of 6 years or under, 10 cc is given intramuscularly within five days after exposure. For children between 7 and 12 years of age 15 cc is given and for older children and adults 20 cc is given in like manner.

Whether the serum is given for prevention or modification depends on the number of days the patient has been exposed. If prevention is desired, however, the dosage may have to be increased corresponding to the increase in days after exposure of the patient. If injection is made on the sixth or seventh day after exposure, a high percentage of patients have a modified type of measles which is followed by lasting immunity. It is probable that serum given after the seventh day following the initial exposure has little effect in either preventing or modifying the disease.

The serum may be given either intravenously or intramuscularly. Vacuum dried serum should be given only intramuscularly.

MILWAUKEE CONVALESCENT SERUM CENTER, COLUMBIA HOSPITAL

Measles Immune Serum (Human) 5 cc and 7.5 cc vials
Preserved with merthiolate 1:10,000

SAMUEL DEUTSCH SERUM CENTER, MICHAEL REESE HOSPITAL

Human Convalescent Measles Serum 5 cc 7.5 cc and 20 cc vials Preserved with phenylmercuric borate 1:15,000

HUMAN SCARLET FEVER IMMUNE SERUM—Scarlet Fever Convalescent Serum—Human Scarlet Fever Immune Serum is a sterile serum obtained from the bloods of healthy individuals (*Homo sapiens*) who have survived an attack of scarlet fever. It complies with the requirements of the National Institute of Health of the United States Public Health Service. *U S P*

For description and standards see the U S Pharmacopeia under Human Scarlet Fever Immune Serum

Actions and Uses—Human scarlet fever immune serum is of value in transferring passive immunity to a patient exposed to scarlet fever. The evidence as to therapeutic activity is conflicting. It may be used in patients sensitive to horse serum though the antitoxic content of convalescent serum is low. It does not seem wholly adequate to meet septic complications.

Dosage—For prophylaxis in infants and young children under 6 years of age 10 cc amounts are given for children between 6 and 12 years of age 15 cc and over 12 years of age and for adults 15 to 20 cc amounts are given intramuscularly. If the individual is continuously exposed it is recommended that a second dose be given ten days after the first injection.

MILWAUKEE CONVALESCENT SERUM CENTER COLUMBIA HOSPITAL

Scarlet Fever Immune Serum (Human) 10 cc and 20 cc vials Preserved with merthiolate 1:10,000

THE PHILADELPHIA SERUM EXCHANGE, THE CHILDREN'S HOSPITAL OF PHILADELPHIA

Scarlet Fever Immune Serum (Human) Containing sufficient amounts of frozen and dried serum (preserved with merthiolate 1:35,000) to furnish 10 cc 15 cc and 20 cc of restored serum packaged with 10 cc containers of sterile distilled water for dilution.

SAMUEL DEUTSCH SERUM CENTER MICHAEL REESE HOSPITAL

Human Convalescent Scarlet Fever Serum 10 cc and 20 cc vials Preserved with merthiolate 1:10,000

VACCINES

(Agents for Producing Active Immunity)

The use of substances for the production of active immunity has the following advantages over passive immunization (use of serums) (a) the antibodies are formed in the patient's own tissues and are not eliminated from the patient's system as rapidly as are antibodies which are contained in serum from another species, for example, the protection conferred by vaccination against smallpox lasts for years, while the prophylactic action of diphtheria antitoxin lasts only two or three weeks. (b) not only are the immune mechanisms of the blood made available but the fixed cells of the body may also take part in the immunization process. (c) an individual who has been actively immunized by the administration of a vaccine reacts more quickly and to a greater extent than a normal individual or an individual previously passively immunized on a subsequent encounter with the antigen. The second response may be against a subsequent dose of the vaccine or an exposure to the antigenic substance in nature.

On the other hand active immunization is not without its limitations. Considerable time, a matter of several days and even weeks is required for active immunity to develop in an individual in response to the administration of a vaccine. Often it is necessary for the person to have immediate protection against a disease as in the case of a known exposure to the disease. Not all individuals respond to a vaccine some acquiring a more effective resistance than others. A patient's body may already be overloaded with antigens as the result of the disease and the introduction of additional antigens sufficient for an immune response in a normal individual might in itself prove harmful to the patient.

Antigens may be of various sorts. The vaccine may be the living virus but in an attenuated form as for example small pox vaccine which is the living virus of smallpox attenuated by passage through the bovine species. The antigenic substances more commonly are dead bacterial cells as for example the extensively used typhoid vaccine. Not infrequently the antigenic substances are products of the bacterial cells such as the bacterial toxins. In recent times it has been found possible to destroy the toxic effect of bacterial toxins without destroying their ability to stimulate antibody production when introduced into the animal body. Examples of this are toxin antitoxin mixture and the various toxoids.

Attenuated Living Viruses or Killed Viruses

RABIES VACCINE — Antirabic Vaccine — Antirabic Virus — Pasteur Treatment — Pasteur Prophylactic — An uncoagulated suspension of the attenuated diluted dried or dead fixed virus of rabies. The virus is obtained from the tissue

of the central nervous system of an animal suffering from fixed virus rabies infection. It complies with the requirements of the National Institute of Health of the United States Public Health Service U S P

For description and standards see the U S Pharmacopeia under Rabies Vaccine

Actions and Uses—By treatment with rabies vaccine after the bite of a rabid animal immunity is often established before the incubation period of the disease is completed and rabies is thus prevented. The treatment fails not infrequently and in a small percentage of cases it is followed by paralysis which is usually transient but rarely may be permanent or even fatal.

RABIES VACCINE (HARRIS)—Brains and spinal cords of rabbits killed after complete paralysis following infection with fixed virus are ground to a paste frozen with carbon dioxide snow and rapidly dried *in vacuo*. The resulting dry powder is standardized by the method devised by Dr. Harris and stored *in vacuo* in the cold. One dose is given daily over a period of 10 days or more doses increasing in unitage up to a maximum.

DR. D. L. HARRIS LABORATORY

Rabies Vaccine (Harris) Vacuum sealed tubes packaged in series of ten consecutive doses of increasing potency, with ten vials of physiological solution of sodium chloride to prepare the vaccine suspension and a Luer syringe with needle.

ELI LILLY AND COMPANY

Rabies Vaccine (Harris) 0.5 cc vials packaged in series of fourteen consecutive doses of increasing potency with a special syringe unit.

RABIES VACCINE (PASTEUR)—(PASTEUR ANTIRABIC VACCINE)—The virus is prepared in accordance with the general method of the U S Public Health Service. One fifth of an inch of dried cord emulsified in 0.6 cc of 60 per cent glycerin containing 0.3 per cent tricresol is supplied.

Actions and Uses—Rabies vaccine (Pasteur) is employed for the prophylaxis of rabies.

Dosage—Prophylactic treatment consists of twenty one doses which are administered at twenty four hour intervals and these are sent in three installments of seven doses each. The installments are sent by special delivery mail. The first dose consists of two sections of a cord dried for six days the second dose consists of two sections of a cord dried for five days and

the third dose two sections of a cord dried for four days. The remaining eighteen doses are prepared from single sections of cords dried as follows 3, 3, 2, 2, 1, 5, 4, 4, 3, 3, 2, 2, 4, 3, 2, 3, 2, 1 days. They are administered in the order listed. Each dose of the dried cord is diluted with 25 cc of sterile sodium chloride solution in the syringe at the time of injection.

RABIES VACCINE (CUMMING)—The vaccine is prepared after preliminary treatment with formalin by dialyzing a 1 per cent suspension of brain tissues from a rabbit dying of rabies (induced by an infection of fixed virus) against running water until the active, virulent virus is destroyed.

Actions, Uses and Dosage—When employed for the prophylaxis of rabies the treatment is divided into two classes: mild requiring 14 doses; severe requiring 21 doses. One dose, 2 cc is given daily over a period of either 14 or 21 days.

RABIES VACCINE (SEMPLÉ)—An antirabic vaccine prepared according to the general method of David Semplé (phenol killed). The brains or brains and spinal cords of rabbits killed on about the sixth day after inoculation with the fixed virus of rabies are triturated with isotonic solution of sodium chloride containing 1 per cent phenol. Various concentrations of nerve tissue are employed. The mixture is strained incubated at 37° C for (usually) 24 hours and then diluted with an equal volume of physiological solution of sodium chloride so that the finished product contains a definite amount of brain substance and about 0.5 per cent phenol. Put up in containers each containing usually sufficient material for a daily dose.

Actions and Uses—Rabies vaccine (Semplé) is used in the prophylactic treatment of rabies.

Dosage—0.5 cc, 1 cc, 2 cc or 3 cc of the suspended vaccine (depending on the dilution employed) daily over a period of from seven to twenty-eight days depending on the site and severity of the injury. The potency of each dose is approximately the same irrespective of the volume of the suspension in which it is supplied.

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LEDERLE LABORATORIES INC

Rabies Vaccine (Semple Method) 2 cc vials packaged in units of seven and fourteen vials Preserved with 0.25 per cent of phenol and 1:20,000 merthiolate

MEDICAL ARTS LABORATORY

Rabies Vaccine (Killed Virus) 2 cc vials packaged in units of seven and fourteen vials Preserved with 0.5 per cent of phenol

NATIONAL DRUG COMPANY

Rabies Vaccine Human (Phenol Killed) 0.5 cc vials in packages of seven without syringe and packages of fourteen with syringe Preserved with 0.5 per cent of phenol

PITMAN MOORE COMPANY

Rabies Vaccine (Killed Virus) Semple Method 1 cc vials packaged in units of seven vials Preserved with 0.25 per cent of phenol and merthiolate 1:20,000

SHARP & DOHME, INC

Rabies Vaccine (Phenol Killed) 0.5 cc vials containing a 25 per cent brain tissue suspension packaged in units of seven vials without syringe and in units of fourteen vials with or without syringe

E. R. SQUIBB & SONS

Rabies Vaccine (Semple Method) 2 cc vials packaged in units of fourteen vials with syringe and needles Also packaged in units of seven vials each containing 2 cc Preserved with 0.5 per cent of phenol

TERRILL'S LABORATORIES

Rabies Vaccine (Phenolized) 3 cc vials containing 4 per cent of brain substance packaged in units of fourteen and twenty one vials Preserved with 0.5 per cent of phenol

U. S. STANDARD PRODUCTS CO

Rabies Vaccine (Semple) 0.5 cc vials packaged in units of seven and fourteen vials, 1 cc vials packaged in units of fourteen vials 2 cc vials and 2 cc syringes each packaged in units of seven and fourteen vials or syringes and the latter in units of twenty one syringes Preserved with 0.5 per cent of phenol

WYETH INCORPORATED

Rabies Vaccine (Semple Method) 2 cc vials and 2 cc syringes each packaged in units of fourteen vials or syringes respectively Preserved with 0.5 per cent of phenol

Rabies Vaccine (Modified Semple Method) • 0.5 cc vials packaged in units of seven and fourteen vials Preserved with 0.5 per cent of phenol

RABIES VACCINE, CHLOROFORM KILLED—Antirabic vaccine prepared according to a modification of the method of David Semple in which the virus is killed with chloroform instead of phenol The brains and spinal cords of rabbits killed on the sixth or seventh day after inoculation with fixed rabies virus are ground with solution of sodium chloride containing 2 per cent chloroform, to yield a 25 per cent suspension of brain and cord substance The suspension is then placed in the refrigerator at 2 to 5 C for two months It is then tested for absence of living virus by rabbit injection The finished product represents a 25 per cent emulsion

Actions, Uses and Dosage—Same as Rabies Vaccine (Semple)

WYETH, INCORPORATED

Rabies Vaccine (Chloroform Killed Virus) • 0.5 cc vials packaged in units of seven and fourteen vials

Bacterial Toxins

Bacterial toxins are sterile solutions obtained by filtering fluid cultures of the microorganisms through bacteria excluding filters The filtrate of toxin contains, in addition to the true bacterial toxin produced during the growth of the microorganisms, metabolic products liberated by the microorganisms during their growth in the medium, soluble components of the bacterial cells, and the unused portions of the culture medium

SCARLET FEVER STREPTOCOCCUS TOXIN—Scarlet Fever Streptococcus Toxin—Scarlet Fever Toxin for Immunization and for the Dick Test—"Scarlet Fever Streptococcus Toxin is a sterile solution in a medium containing not more than 1 per cent of peptone but no meat extractive, of certain products including a soluble toxin resulting from the growth in the broth of suitable strains of hemolytic streptococci (*Streptococcus scarlatinae*) It complies with the requirements of the National Institute of Health of the United States Public Health Service" *U S P*

For description and standards see the *U S Pharmacopeia* under Scarlet Fever Streptococcus Toxin

For diagnostic scarlet fever preparations see under Diagnostic Agents

Actions, Uses and Dosage—The toxin is used for active immunization For this purpose it is injected subcutaneously at weekly intervals The amount of toxin necessary for immunity production varies with the individual Five to six doses are

given beginning with 162 to 650 skin test doses for the first injection and increasing the amount of toxin in each subsequent injection to a final dose of 100 000 to 120 000 skin test doses. Immunity to the toxin appears in a few weeks and is determined by the absence of a reaction to the intracutaneous test.

FEDERLE LABORATORIES INC.

Scarlet Fever Streptococcus Immunizing Toxin 1 cc and 10 cc vials (single and ten immunization doses respectively), each packaged in units of five vials containing respectively 650 2 500 10 000 30 000 and 100 000 120 000 skin test doses per cubic centimeter also the 1 cc vial containing 100 000 120 000 skin test doses is packaged separately. Preserved with 0.4 per cent phenol.

NATIONAL DRUG COMPANY

Scarlet Fever Streptococcus Toxin for Immunization 1 cc vials packaged in units of five vials containing respectively, 650 2 500 10 000, 30 000 and 100 000 120 000 skin test doses per cubic centimeter. 10 cc vials packaged in units of six vials containing respectively 650 2 500 10 000 30 000 100 000 120 000 and 100 000 120 000 skin test doses per cubic centimeter. Preserved with 0.5 per cent phenol.

PANKE, DAVIS & COMPANY

Scarlet Fever Streptococcus Toxin for Immunization 1 cc vials packaged in units of five vials containing respectively 650 2 500 10 000 30 000 and 100 000 120 000 skin test doses per cubic centimeter, 10 cc vials packaged in units of six vials containing respectively 650 2 500 10 000 30 000 100 000 120 000 and 100 000 120 000 skin test doses per cubic centimeter.

SHARP & DOHME INC.

Scarlet Fever Streptococcus Toxin for Immunization 1 cc. and 10 cc vials (single and ten immunization doses respectively) each packaged in units of five vials containing respectively, 650 2 500 10 000 30 000 and 100 000 120 000 skin test doses per cubic centimeter the 1 cc vial containing 100 000 120 000 skin test doses is also packaged separately.

E. R. SQUIBB & SONS

Scarlet Fever Streptococcus Toxin for Immunization 1 cc vials packaged in units of five vials containing respectively, 650 2 500 10 000 30 000 and 100 000 120 000 skin test doses per cubic centimeter. 10 cc. vials packaged in units of five vials containing respectively 650 2 500 10 000 30 000 and

100 000 120 000 skin test doses per cubic centimeter and in single vial packages containing 100 000 120 000 skin test doses. Preserved with 0.5 per cent of phenol and buffered with KH_2PO_4 and NaOH .

U S STANDARD PRODUCTS CO

Scarlet Fever Streptococcus Toxin for Immunization
1 cc vials packaged in units of five vials containing respectively, 650 2 500 10 000 30 000 and 100 000 120 000 skin test doses per cubic centimeter. 10 cc vials packaged in units of six vials containing respectively 650 2 500 10 000 30 000 100 000 120 000 and 100 000 120 000 skin test doses per cubic centimeter. Preserved with phenol 0.5 per cent.

| | | |
|---|-----|--------------|
| SCARLET FC | - - | TOXIN |
| TANNIC ACID | | buffered |
| solution containing 1 | | ipitate of |
| scarlet fever toxin and 0.4 per cent phenol as a preservative | | |

Actions and Uses—This tannic acid precipitated toxin is claimed to permit slower absorption and a prolonged antigenic stimulus which permits a reduction in the amount of toxin and size of dose as compared with former methods of immunization.

Dosage—Children receive three intracutaneous injections of 0.1 cc (dose 1 750 STD/0.1 cc dose 2 3 000 STD/0.1 cc dose 3 10 000 STD/0.1 cc) at two week intervals. Some may need a supplemental dose after a four week interval.

Adults may receive 500 2 000 6 000 and 10 000 STD at two week intervals. Each vial should be well shaken before use. The toxin should not be used beyond expiration date on label or if it does not resuspend completely on shaking.

Preparation—Scarlet fever toxin is prepared from cultures of hemolytic streptococcus N Y 5 (Dochiez) strain and treated with ammonium sulfate. The ammonium sulfate precipitate is dissolved in sterile saline solution buffered at pH 6.6 and preserved with phenol. Samples of the toxin which meet the requirements of the National Institute of Health are further treated by the addition of sterile diluent and 0.5 per cent solution of tannic acid.

The tannic acid precipitated toxin is washed free of tannic acid and suspended in buffered saline solution containing 1 per cent acacia. The suspension is assayed for skin test dose potency and diluted suitably for market packaging. The finished product is preserved with 0.4 per cent phenol and complies with the requirements of the National Institute of Health of the United States Public Health Service.

WYETH INCORPORATED

Scarlet Fever Streptococcus Toxin for Immunization
Tannic Acid Precipitated 0.5 cc single immunization vials and 2 cc 10 immunization vials packaged in units of three vials

(children) contains respectively in each 0.1 cc 750, 3 000 and 10 000 skin test doses and in units of four vials (adult) containing in each 0.1 cc 500 2000, 6000 and 10 000 skin test doses. Also 0.5 cc single and 2 cc ten dose vials containing a supplementary dose for children and adults representing in each 0.1 cc 10 000 skin test doses. Preserved with phenol 0.4 per cent.

Bacterial Toxins, Modified

Certain bacterial toxins may be modified so as to retain their capacity for bringing about an immune response while at the same time they are made relatively harmless or at least their toxicity is greatly decreased. Examples of such modified bacterial toxins are Diphtheria Toxin Antitoxin Mixture and Diphtheria Toxoid.

Toxin Antitoxin Mixture

DIPHTHERIA TOXIN-ANTITOXIN MIXTURE—
Mistura Toxini Diphtherici et Antitoxini Diphtherici
—A mixture of diphtheria toxin and diphtheria antitoxin. Labelled to show the volume of each dose and the amount of L+ doses of toxin contained in each dose. Each 1 cc represents 0.1 L+ dose of diphtheria toxin neutralized with a proper amount of diphtheria antitoxin.

The product should be used only if clear and free from sediment or flocculi.

The antitoxin used in diphtheria toxin antitoxin mixture is produced from the horse, goat or sheep. Diphtheria toxin antitoxin mixture has been largely supplanted by diphtheria toxoid.

Actions, Uses and Dosage—Diphtheria toxin antitoxin mixture is used for active immunization against diphtheria. It is employed chiefly for those who react severely to toxoid, principally older children and adults. Ordinarily diphtheria toxoid is preferred. It is administered subcutaneously, preferably at the insertion of the deltoid, in three doses with an interval of one week between doses. A Schick test performed about six months after the last injection determines whether further immunization is necessary. In the presence of an outbreak of diphtheria an immunizing dose of diphtheria antitoxin alone should be used if exposed children cannot be kept under regular medical observation.

PARKE, DAVIS & COMPANY

Diphtheria Toxin Antitoxin Mixture (Goat) 1 cc bulb and 30 cc vial

WYETH INCORPORATED

Diphtheria Toxin-Antitoxin Mixture 1 cc, 10 cc 20 cc and 30 cc ampuls and 1 cc syringe

Diphtheria Toxin-Antitoxin Mixture (Goat) 1 cc 10 cc 20 cc and 30 cc vials

Toxoids

DIPHTHERIA TOXOID — Anatoxin Ramon — Diphtheria Anatoxin — A sterile aqueous solution of the products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*) so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs but retaining the property of inducing active immunity. The toxicity of the Diphtheria Toxoid shall be so low that five times the dose for the adult human does not cause either local or general symptoms of diphtheria poisoning in a guinea pig within thirty days after its injection into the animal. The antigenic value shall be such that the initial dose for the human shall protect at least 80 per cent of guinea pigs six weeks after injection against five minimum lethal doses each of diphtheria test toxin. Diphtheria Toxoid complies with the requirements of the National Institute of Health of the United States Public Health Service U S P

For description and standards see the U S Pharmacopeia under Diphtheria Toxoid

Actions Uses and Dosage — Diphtheria toxoid is used for active immunization against diphtheria. It is administered subcutaneously preferably at the insertion of the deltoid in two or three doses of 1 cc each with an interval of three or four weeks between doses. Since some local and general reactions have been observed in adults and in children over 8 years of age an intracutaneous test dose of 0.1 cc of the toxoid diluted (1 in 20) with physiological saline solution should be given to determine sensitivity in such persons

CUTTER LABORATORIES

Diphtheria Toxoid 1 cc 10 cc and 30 cc vials in packages of two and of 20 1 cc vials one 10 cc vial and one 30 cc vial Preserved with 1 10 000 merthiolate

FEDERLE LABORATORIES INC

Diphtheria Toxoid 1 cc and 30 cc vials in packages of three 1 cc vials and one 30 cc vial Each package is accompanied by a vial containing sufficient diluted diphtheria toxoid for ten sensitivity tests

ELI LILLY AND COMPANY

Diphtheria Toxoid 1 cc and 30 cc vials in packages of two 1 cc vials and one 30 cc vial Preserved with 1 10 000 merthiolate

NATIONAL DRUG COMPANY

Diphtheria Toxoid 3 cc vials (one immunization) and 30 cc vials Preserved with 1 10 000 merthiolate

PARKE DAVIS & COMPANY

Diphtheria Toxoid 1 cc and 30 cc vials in packages containing one 3 cc vial one 1 cc vial and one 30 cc vial

SHARP & DOHME INC

Diphtheria Toxoid Vials of 3 cc (1 three dose immunization) and 30 cc (10 three dose immunizations)

E R SQUIBB & SONS

Diphtheria Toxoid 1 cc ampuls in packages of three and 30 cc vial in single packages Preserved with 1 10 000 merthiolate

Diphtheria Toxoid for Reaction Test 1 cc vial containing sufficient for ten tests

U S STANDARD PRODUCTS CO

Diphtheria Toxoid 1 cc 60 cc 20 cc and 30 cc vials in packages of two 1 cc vials one 6 cc vial one 20 cc vial and one 30 cc vial

WYETH, INCORPORATED

Diphtheria Toxoid 1 cc and 30 cc vials in packages of two and of twenty 1 cc vials and one 30 cc vial Each package is accompanied by a sufficient amount of diluted diphtheria toxoid for the reaction test

DIPHTHERIA TOXOID, ALUM PRECIPITATED

--Refined Diphtheria Toxoid A turbid white slightly gray or slightly pink suspension prepared by adding a sterile aqueous solution of alum to Diphtheria Toxoid washing the resultant precipitate with isotonic solution of sodium chloride, and resuspending it in isotonic solution of sodium chloride to which a suitable preservative may be added *U S P*

For description and standards see the U S Pharmacopeia under Diphtheria Toxoid Alum Precipitated

Actions Uses and Dosage—Diphtheria toxoid, alum precipitated is used for active immunization against diphtheria. It is administered subcutaneously preferably at the insertion of the deltoid muscle. Because of the physical character of the product absorption is delayed. Two doses or more of 0.5 cc (or 1 cc if this amount is necessary to furnish two units of

antitoxin) with an interval of 4 to 6 weeks are advisable to obtain a reversal of the Schick reaction although a single dose sometimes is sufficient. A nodule persists at the site of inoculation for several days and rarely an abscess forms.

CUTTER LABORATORIES

Diphtheria Toxoid, Alum Precipitated, Refined 1 cc and 10 cc vials Preserved with 1:10,000 merthiolate

LEDERLE LABORATORIES, INC

Refined Diphtheria Toxoid Alum Precipitated 0.5 cc, 1 cc and 5 cc vials in packages of two 0.5 cc vials, two 1 cc vials, one 5 cc vial and one 10 cc vial Preserved with merthiolate 1:10,000

ELI LILLY AND COMPANY

Diphtheria Toxoid, Alum Precipitated 0.5 cc and 5 cc vials

NATIONAL DRUG COMPANY

Diphtheria Toxoid adjusted (supplementary) and one 5 cc vial (five doses) 1:10,000 with merthiolate

PARKE, DAVIS & COMPANY

Diphtheria Toxoid Alum Precipitated (Refined) 0.5 cc and 5 cc vials containing one and ten doses respectively 1 cc and 10 cc vials containing one and ten doses respectively Preserved with 1:10,000 merthiolate

PITMAN MOORE COMPANY

Diphtheria Toxoid (Alum Precipitated Refined) Two 1 cc vials (2 doses) and 10 cc vials (10 doses) Preserved with 1:10,000 merthiolate

SHARP & DOHME INC

Diphtheria Toxoid Alum Precipitated Refined Vials of 5 cc (5 immunizations, two 0.5 cc doses per immunization), 2 cc (1 two dose immunization) and 10 cc (5 two dose immunizations)

E. R. SQUIBB & SONS

Refined Diphtheria Toxoid, Alum Precipitated 1 cc vial in packages of two vials sufficient for one immunization and 10 cc vials for five immunizations. A more concentrated

product is also available to be given preferably in injections of 0.5 cc each packages of two 0.5 cc vials sufficient for one immunization and 50 cc vial sufficient for 5 immunizations Preserved with 1:10,000 merthiolate

U S STANDARD PRODUCTS CO

Diphtheria Toxoid Alum Precipitated Refined 1 cc and 10 cc vials in packages of one and of ten 1 cc vials and one 10 cc vial Preserved with 1:10,000 merthiolate

WYETH INCORPORATED

Diphtheria Toxoid Alum Precipitated (Refined) 0.5 cc 1 cc 5 cc and 10 cc vials in packages of one and of ten 0.5 cc vials one and ten 1 cc vials one 5 cc vial and one 10 cc vial Preserved with 1:10,000 merthiolate

DIPHTHERIA TOXOID, TETANUS TOXOID ALUM PRECIPITATED, COMBINED—Combined diphtheria toxoid and tetanus toxoid alum precipitated

Actions Uses and Dosage—Same as for Diphtheria Toxoid and tetanus Toxoid Alum Precipitated (Refined) except that single doses are generally 1 cc in volume

LEDERLE LABORATORIES INC

Refined Diphtheria Tetanus Toxoid Alum Precipitated 1 cc and 10 cc vials in packages of two 1 cc vials and of one 10 cc vial

ELI LILLY AND COMPANY

Combined Diphtheria Toxoid Tetanus Toxoid Alum Precipitated 1 cc and 10 cc vials in packages of two 1 cc vials and of one 10 cc vial

NATIONAL DRUG COMPANY

Diphtheria and Tetanus Toxoids Combined Alum Precipitated One immunization in packages of two 1 cc vials and five immunizations in packages of two 5 cc vials Preserved with 1:10,000 merthiolate

PARKE DAVIS & COMPANY

Diphtheria Tetanus Toxoid (Combined) Packages of three 2 cc vials and packages of one 30 cc vial

Diphtheria Tetanus Toxoid (Combined) Alum Precipitated 1 cc vial Preserved with 1:20,000 phenol

L. R. SQUIBB & SONS

Combined Diphtheria Toxoid Tetanus Toxoid Alum Precipitated 1 cc and 10 cc vials in packages of two 1 cc vials and of one 10 cc vial

WYETH, INCORPORATED

Combined Diphtheria Tetanus Toxoid, Alum Precipitated 1 cc and 10 cc vials in packages of two 1 cc vials and of one 10 cc vial

STAPHYLOCOCCUS TOXOID—*Staphylococcus* Ana toxin—Univalent or polyvalent potently hemolytic and dermo necrotic toxins of *Staphylococcus aureus* and *albus* altered by the formaldehyde detoxifying process of Burnett (modified from Ramon). Antigenicity is maintained but toxicity is greatly diminished. The antigenic potency is determined by injecting 1 cc of toxoid per kilogram intravenously into three rabbits and the resulting serum tested at the end of one and two weeks for its content of staphylococcus antitoxin. No staphylococcus toxoid is used which in doses of 0.2 cc or less of the undiluted material will cause necrosis when injected into rabbits. The toxin is titrated to determine its dermonecrotic potency.

Actions Uses and Dosage—*Staphylococcus* toxoid has been reported a valuable agent in the prophylaxis and therapy of various staphylococcic pyodermas and localized pyogenic processes due to *Staphylococcus aureus* and *albus* (boil carbuncle furunculosis acne and so on). The toxoid is said to be effective in producing active immunity to the dermonecrotic and hemolytic elements of the toxins of *Staphylococcus aureus* and *albus* irrespective of the individual strain of the infecting organism. The toxoid induces the production of staphylococcus antitoxin in the blood serum of immunized persons.

The initial dose should be not more than 0.1 cc containing 10 skin necrotizing doses injected subcutaneously at the insertion of the deltoid. Subsequent doses at weekly intervals should be increased by 10 to 20 skin necrotizing doses. Marked local or a systemic reaction to any dose contraindicates increase of the succeeding dose.

AYERST McKINNA & HARRISON LTD

Staphylococcus Toxoid 3 cc vials containing in each cubic centimeter the toxoid derived from 20,000 necrotizing doses of toxin. Preserved with 1:20,000 merthiolate.

LEDERLE LABORATORIES INC

Staphylococcus Toxoid Two 5 cc vials one containing 100 necrotizing doses and one containing 1,000 necrotizing doses of toxin.

NATIONAL DRUG COMPANY

Staphylococcus Toxoid Two 5 cc vials one containing 100 necrotizing doses and one containing 1 000 necrotizing doses of toxin

PARKE, DAVIS & COMPANY

Staphylococcus Toxoid Two 5 cc vials one containing 100 necrotizing doses and one containing 1 000 necrotizing doses of toxin

PITMAN MOORE COMPANY

Staphylococcus Toxoid 5 cc vials containing in each cubic centimeter the toxoid derived from 1 000 necrotizing dose of toxin Preserved with 1 10 000 merthiolate

SHARP & DOHME, INC

Staphylococcus Toxoid Two 5 cc vials containing in each cubic centimeter the toxoid derived from 100 and 1 000 necrotizing doses of toxin, respectively Preserved with ortho chloromercuriphenol 1 40 000

E R SQUIBB & SONS

Staphylococcus Toxoid 5 cc vial containing in each cubic centimeter the toxoid derived from 1 000 necrotizing doses of toxin. Preserved with 1 10 000 merthiolate

TETANUS TOXOID—Tetanus Toxoid is a sterile solution of the product of growth of the tetanus bacillus (*Clostridium tetani*) so modified by treatment with solution of formaldehyde as to have lost the ability to cause toxic effects in guinea pigs but retaining the property of inducing active immunity

The toxicity of Tetanus Toxoid shall be so low that 5 cc. of the material does not cause any symptoms of tetanus in a guinea pig within a period of twenty one days after its injection into the animal The antigenic value shall be such that 1 cc of the material six weeks after injection shall protect at least 80 per cent of guinea pigs from all symptoms of tetanus for a period of ten days after the injection of 10 minimum lethal doses of tetanus test toxin into each animal

Actions, Uses and Dosage—To protect against infection three doses of 1 cc. each intramuscularly or subcutaneously with an interval of three weeks between injections An additional dose of 1 cc should be given at the time of injury or infection Active immunization of the tetanus would appear to be a desirable procedure in the case of individuals who are subject to a greater than normal hazard of the disease

LEDERLE LABORATORIES, INC

Tetanus Toxoid (Fluid) 1 cc and 30 cc vials in packages of three 1 cc vials and one 30 cc vial

E R SQUIRRE & SONS

Tetanus Toxoid 1 cc 3 cc and 30 cc rubber diaphragm capped vials

TETANUS TOXOID ALUM PRECIPITATED —

Refined Tetanus Toxoid — Alum Precipitated Tetanus Toxoid is a turbid white or slightly gray suspension prepared by adding a sterile aqueous solution of alum to Tetanus Toxoid washing the resultant precipitate with isotonic solution of sodium chloride and resuspending it in isotonic solution of sodium chloride to which a suitable preservative may be added *U S P*

For description and standards see the *U S Pharmacopeia* under Tetanus Toxoid Alum Precipitated

Actions Uses and Dosage—Tetanus toxoid is recommended for the production of active immunity to tetanus. The recommended human dose (10 cc or 0.5 cc) is injected subcutaneously preferably in the region of the deltoid. Approximately three months later the second and final injection is given. The immunity thus produced is reasonably persistent. However it has been shown that at some time after the original immunization a single injection of toxoid is given there results a prompt (within two weeks) and marked rise in the antitoxic titer of the serum. Thus in cases of injury to persons previously immunized an injection of tetanus toxoid may suffice to protect against tetanus in place of the usual tetanus antitoxin. It should be borne in mind that in these cases several weeks is required following the second injection of toxoid before immunity may be assumed to be well established. Therefore in any dubious instance the conservative course is the administration of antitoxin. Active immunization of tetanus would appear to be a desirable procedure in the case of individuals who are subject to a greater than normal hazard of the disease.

LEDERLE LABORATORIES, INC

Refined Alum Precipitated Tetanus Toxoid 1 cc and 10 cc vials in packages of two 1 cc vials (two immunizing doses) and of one 10 cc vial (ten immunizing doses). Preserved with merthiolate 1:10,000

ELI LILLY AND COMPANY

Tetanus Toxoid Alum Precipitated 0.5 cc and 5 cc vials in packages of two cc vials (two immunizing doses) and of one 5 cc vial (ten immunizing doses)

NATIONAL DRUG COMPANY

Tetanus Toxoid (Alum Precipitated) 1 cc and 10 cc vials in packages of two 1 cc vials (one immunization) one 10 cc vial (five immunizations) and one 1 cc vial for subsequent dosage Preserved with merthiolate 1 10 000

PARKE DAVIS & COMPANY

Tetanus Toxoid, Alum Precipitated (Refined) Two 1 cc vials (one immunization treatment) and one 10 cc vial (five immunization treatments)

PITMAN MOORE COMPANY

Tetanus Toxoid (Alum Precipitated) 1 cc vials in packages of two 1 cc vials (two immunizing doses) and 10 cc vial (ten immunizing doses) Preserved with merthiolate 1 10 000

SHARP & DOHME INC

Tetanus Toxoid Alum Precipitated, Refined 1 cc and 10 cc vials in packages of two 1 cc vials (one immunization) and of one 10 cc vial (five immunizations) Preserved with orthochloromercuriphenol 1 20 000

E R SQUIBB & SONS

Refined Tetanus Toxoid Alum Precipitated 1 cc vials in packages of two each (two immunizing doses) 10 cc vials (ten immunizing doses) Preserved with 1 10 000 merthiolate

WYETH INCORPORATED

Tetanus Toxoid Alum Precipitated (Refined) 0.5 cc and 1 cc vials in packages of two 0.5 cc vials (two immunizing doses) and of two 1 cc vials (two immunizing doses), 5 cc vial (five immunizing doses) 10 cc vial (five immunizing doses) and 10 cc vial (ten immunizing doses) Preserved with merthiolate 1 10 000

Bacterial Vaccines

Bacterial vaccines or bacterins are suspensions of killed bacteria in physiological solution of sodium chloride usually with the addition of some preservative such as cresol or phenol

The dosage and intervals for bacterial vaccine treatment cannot be stated definitely In general the severer the disease the smaller the dose should be, and the smaller the doses the shorter the intervals In mild affections no improvement may result until the vaccine is pushed to a systemic reaction

Prophylactically the typhoid and paratyphoid vaccines apparently have proved of great value as compared to other stock bacterial vaccines the therapeutic use of which often rests on uncertain clinical evidence. Plague and cholera vaccines are also used in prophylaxis.

BACTERIAL VACCINE MADE FROM BRUCELLA (Undulant Fever Vaccine)—A bacterial vaccine obtained from *Brucella melitensis*, *Br. abortus* or *Br. suis*. No potency tests are made. Purity of cultures is determined by the study of colony formation, carbohydrate reactions and agglutination test with specific serum.

Actions and Uses—Undulant fever vaccine is proposed for use in the treatment of undulant fever.

Dosage—Subcutaneously or intramuscularly, 0.1 cc. to 0.25 cc. of the vaccine containing 2 to 6 billion killed organisms is used for the initial dose. Subsequent doses are gradually increased by the amount of the initial dose and may be administered at two to five day intervals until a dose of 1 cc. is reached. Further vaccine should not be given to the patient after a strong constitutional reaction has been obtained until several weeks have elapsed to determine whether the patient requires any further treatment.

JENSEN SALSBERG LABORATORIES, INC.

Undulant Fever Bacterial Vaccine 1 cc. vial. Each 1 cc. contains 3 billion each of killed *Br. abortus* and *Br. suis* in physiological solution of sodium chloride preserved with 0.5 per cent of phenol.

FEDERLE LABORATORIES, INC.

Undulant Fever Vaccine 5 cc. vial. Each 1 cc. contains 1,000 million each of killed *Br. abortus* and *Br. suis* in isotonic solution of sodium chloride preserved with 0.5 per cent of phenol.

NATIONAL DRUG COMPANY

Undulant Fever Vaccine (*Abortus* and *Suis*) 30 cc. vials. Each 1 cc. contains 2,500 million each of killed *Br. abortus* (bovine) and *Br. suis* (porcine) preserved with 1:10,000 merthiolate.

PITMAN MOORE COMPANY

Undulant Fever Vaccine, *Abortus* and *Suis* 6 cc. and 20 cc. diaphragm stoppered vials. Each cubic centimeter contains 1,000 million each of killed *Brucella abortus* and *Brucella suis* preserved with 1:10,000 merthiolate.

Undulant Fever Vaccine, Melitensis: 6 cc and 20 cc diaphragm stoppered vials. Each cubic centimeter contains 2,000 million each of killed *Brucella melitensis*, preserved with 1:10,000 merthiolate.

BACTERIAL VACCINE MADE FROM THE CHOLERA VIBRIO (Cholera Vaccine)—Prepared from killed cholera vibrios *Vibrio comma (cholerae)*

Actions, Uses and Dosage.—This vaccine has been used for the prevention of cholera, administered in two or three doses. For the first two doses 0.5 cc. and for the third dose 1 cc. administered subcutaneously at intervals of seven to ten days. A stimulating dose of 1 cc. every six months while danger of infection exists has been suggested. However, the value of this vaccine has not been conclusively established.

FRI JULY & Co

Cholera Vaccine: 20 cc vial Each cubic centimeter contains 8,000 million killed cholera vibrios

**BACTERIAL VACCINE MADE FROM THE
PLAGUE BACILLUS (Plague Bacillus Vaccine) —**
Prepared from killed *Pasteurella pestis*

Actions, Uses and Dosage—This vaccine has been used for the prevention of plague administered in two doses containing 1,000 million and 2,000 million killed bacilli respectively. The value of this vaccine is very doubtful.

BACTERIAL VACCINE MADE FROM STAPHYLOCOCCI (*Staphylococcus Vaccine*).—*Vaccinum Staphylococcicum*—Made from *Staphylococcus aureus*, from *Staphylococcus albus*, or from *Staphylococcus citreus*, or from all three.

Actions and Uses—*Staphylococcus vaccine* is used in carbuncles, abscesses, furuncles, and boils. It is also used in the treatment of skin diseases, such as eczema, psoriasis, and lichen planus. The vaccine is prepared by cultivating the bacteria in a stock vaccine, which is then used to inoculate the patient. The forms of the vaccine are deep seated, the face, the chest, and the back. The vaccine is indolent, the

Dosage—100 million to 1,000 million killed bacteria

ABBOTT LABORATORIES

Staphylococcus Combined Vaccine. 6 cc and 20 cc vials
Each 1 cc contains 1,000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus*

CUTTER LABORATORIES

Staphylococcus Vaccine 5 cc vial Each 1 cc. contains 2 000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus* in physiological solution of sodium chloride preserved with 0.5 per cent of phenol

LEE HILL AND COMPANY

Staphylococcus Vaccine 5 cc. and 20 cc vials Each 1 cc contains 2 000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus* in isotonic solution of sodium chloride preserved with 1:10 000 merthiolate

Staphylococcus Aureus Vaccine 5 cc and 20 cc vials Each 1 cc contains 2 000 million killed *Staphylococcus aureus* Preserved with 1:10 000 merthiolate

NATIONAL DRUG COMPANY

Staphylococcus Vaccine 30 cc vials Each 1 cc contains 1 000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus* in isotonic solution of sodium chloride, preserved with 1:10 000 merthiolate

PARKE DAVIS & COMPANY

Furunculosis Vaccine 5 cc and 20 cc vials Each 1 cc contains 2 000 million killed *Staphylococcus aureus*

Staphylococcus Vaccine (Combined) 1 cc 5 cc and 20 cc vials Each 1 cc contains 1 000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus*

WYETH INCORPORATED

Staphylococcus Vaccine (Albus and Aureus) 5 cc and 10 cc vials Each 1 cc contains 1 000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus* in isotonic solution of sodium chloride preserved with 0.25 per cent of tricresol

BACTERIAL VACCINE MADE FROM THE TYPHOID BACILLUS—Typhoid Prophylactic—Enteric Vaccine—Typhoid Vaccine—A sterile suspension of killed typhoid bacilli (*Eberthella typhosa*) of a strain selected for high antigenic efficiency in isotonic solution of sodium chloride or other suitable diluent. The vaccine shall contain in each cc at least 1 000 000 000 typhoid organisms. It complies with the requirements of the National Institute of Health of the United States Public Health Service U S P

For description and standards see the U S Pharmacopeia under Bacterial Vaccine made from the Typhoid Bacillus

Actions and Uses—Typhoid vaccine is of considerable value in the prevention of typhoid fever. Typhoid vaccine is also used in nonspecific protein therapy, but such use is sometimes attended by dangerous and even fatal reactions.

Dosage—"Average Dose—Hypodermic, for active immunization 0.5 cc and 1 cc, the latter dose to be repeated once"—*U S P*. As a preventive, typhoid vaccine should be administered only to healthy persons. The skin should be sterilized with iodine and an initial dose of 500 million bacteria injected, with aseptic precautions. This injection should be followed in from seven to ten days by a second dose of one billion bacteria and a third injection of the same size is given from seven to ten days after the second.

CUTTER LABORATORIES

Typhoid Prophylactic 1 cc bottles in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain), 20 cc bottles containing 1,000 million killed bacilli of the same strain per cubic centimeter. Preserved with 0.25 per cent tricresol.

ELI LILLY AND COMPANY

Typhoid Vaccine, Prophylactic 1 cc vials in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain) and in packages of ten, each containing 500 million or 1,000 million killed bacilli of the same strain. Preserved with 1:10,000 merthiolate.

NATIONAL DRUG COMPANY

Typhoid Vaccine 1 cc vials in packages of three, one containing 1,000 million and two each containing 2,000 million killed bacilli (strain 58, the Panama carrier strain), 5 cc and 30 cc vials containing 2,000 million killed bacilli of the same strain per cubic centimeter. Preserved with 1:10,000 merthiolate.

PARKE, DAVIS & COMPANY

Typhoid Vaccine (Prophylactic) 1 cc vials in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (Rawlings strain and the Panama strain in equal proportions).

Typhoid Vaccine (Prophylactic) 25 cc vials in packages of ten, and 20 cc vials containing 1,000 million killed bacilli (Rawling's strain and the Panama strain in equal proportions) per cubic centimeter.

U S STANDARD PRODUCTS CO

Typhoid Vaccine 1 cc vials in packages of three one containing 500 million and two each containing 1 000 million killed bacilli (strain 58 the Panama carrier strain) 5 cc and 20 cc vials containing 1 000 million killed bacilli of the same strain per cubic centimeter Preserved with 0.5 per cent of phenol

WYETH, INCORPORATED

Typhoid Vaccine 1 cc vials in packages of three one containing 500 million and two each containing 1 000 million killed bacilli (Rawlings strain or the Panama carrier strain as ordered) and in packages of thirty ten containing 500 million each and twenty containing 1 000 million each of either strain as desired 5 cc 10 cc and 20 cc vials as ordered 50 cc vials containing 1 000 million killed bacilli of either strain per cubic centimeter

BACTERIAL VACCINE MADE FROM THE
TYPHOID BACILLUS AND THE PARATYPHOID

Combined Vaccine—
Typhoid Mixed Vac
Prophylactic—Mixed
aqueous solution of sodium

chloride or other suitable anhydrous salt of typhoid bacilli (*Eberthella typhosa*) of a strain selected for high antigenic efficiency and killed paratyphoid A bacilli (*Salmonella paratyphi*) and killed paratyphoid B bacilli (*Salmonella schottmulleri*)

The vaccine shall contain in 1 cc at least 1 000 000 000 typhoid organisms and at least 250 000 000 of each of the paratyphoid organisms. It meets the requirements of the National Institute of Health of the United States Public Health Service U S P

For description and standards see the U S Pharmacopeia under Bacterial Vaccine Made From The Typhoid Bacillus and The Paratyphoid A and B Bacilli

Actions and Uses—Typhoid Paratyphoid Vaccine is of considerable value in the prevention of typhoid fever and paratyphoid fevers due to *Eberthella typhosa* *Salmonella paratyphi* (*Bacterium paratyphosum A*) and *Salmonella schottmulleri* (*Bacterium paratyphosum B*)

Dosage—Average dose—Hypodermic for active immunization 0.5 cc and 1 cc the latter dose to be repeated once U S P

ABBOTT LABORATORIES

Typhoid Paratyphoid Bacterin (Prophylactic) 1 cc ampuls in packages of three one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 375 million each

of paratyphoid bacilli A and B and two each containing 1 000 million killed typhoid bacilli and 750 million each of killed paratyphoid bacilli A and B

Typhoid-Paratyphoid Bacterin (Prophylactic) 3 cc vials in packages of ten 6 cc and 20 cc vials containing 1 000 million killed typhoid bacilli (Panama carrier strain 58) and 750 million each of killed paratyphoid bacilli A and B per cubic centimeter

CUTLER LABORATORIES

Typhoid-Paratyphoid Prophylactic 1 cc vials in packages of three one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of killed paratyphoid bacilli A and B and two each containing 1 000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B 25 cc syringe and 20 cc vial containing 1 000 million killed typhoid bacilli of the same strain and of 500 million each of killed paratyphoid bacilli A and B per cubic centimeter Preserved with 0.25 per cent of tricresol

LEDERLE LABORATORIES INC

Typhoid Combined Vaccine (Prophylactic) 1 cc vials in packages of three one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of killed paratyphoid bacilli A and B and two each containing 1 000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B 5 cc and 20 cc vials containing in each 1 cc 1 000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B

ELI LILLY AND COMPANY

Typhoid Mixed Vaccine Prophylactic 1 cc vials in packages of three one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of killed paratyphoid bacilli A and B and two each containing 1 000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B and in hospital sets of 10 vials each containing vaccine equivalent to the three 1 cc vials 5 cc and 20 cc vials containing in each 1 cc 1 000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B Preserved with 1 10 000 merthiolate

NATIONAL DRUG COMPANY

Typhoid Paratyphoid Combined Vaccine 1 cc vials in packages of three one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 250 million each of killed

paratyphoid bacilli A and B and two each containing 1 000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B and in packages of thirty ten containing 500 million killed typhoid bacilli of the same strain and 250 million each of killed paratyphoid bacilli A and B and twenty containing twice these amounts 5 cc and 30 cc vials containing in each 1 cc 1 000 million killed typhoid bacilli of the same strain and 500 million each of killed paratyphoid bacilli A and B Preserved with 1 10 000 mer thiolate

PARKE DAVIS & COMPANY

Typhoid Paratyphoid Vaccine (Prophylactic) 1 cc vials in packages of three one containing 500 million killed typhoid bacilli (Rawlings strain and Panama carrier strain 58 in equal proportions) and 250 million each of killed paratyphoid bacilli A and B and two each containing 1 000 million killed typhoid bacilli of the same strain mixture and 500 million each of killed paratyphoid bacilli A and B 25 cc vials in packages of ten and 20 cc vials containing 1 000 million killed typhoid bacilli of the same strain mixture and 500 million each of killed paratyphoid bacilli A and B per cubic centimeter Preserved with 0.3 per cent of tricresol

SHARP & DOHME INC

Typho Bacterin Mixed (Triple Vaccine) Packages of three vials 0.5 cc 1 cc and 1 cc respectively containing 1 000 million killed typhoid bacilli (Panama carrier strain 58) and 500 million each of killed paratyphoid A and B bacilli per cubic centimeter packages of thirty vials 10 of 0.5 cc and 20 of 1 cc containing killed typhoid and paratyphoid A and B bacilli as above 5 cc and 20 cc vials containing killed typhoid and paratyphoid A and B bacilli as above

E. R. SQUIBB & SONS

Typhoid Vaccine Combined Immunizing 1 cc vials in packages of three one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 125 million each of killed paratyphoid bacilli A and B and two each containing 1 000 million killed typhoid bacilli of the same strain and 250 million each of killed paratyphoid bacilli A and B 5 cc and 20 cc vials containing in each 1 cc 1 000 million killed typhoid bacilli of the same strain and 250 million each of killed paratyphoid bacilli A and B Preserved with 0.5 per cent of phenol

THE UPJOHN COMPANY

Typhoid Vaccine 20 cc vials Each
1 (Panama carrier
st typhoid bacilli A
and B Preserved with 0.5 per cent of phenol

U S STANDARD PRODUCTS CO

Typhoid-Paratyphoid Vaccine Combined 1 cc vials in packages of three one containing 500 million killed typhoid bacilli (Panama carrier strain 58) and 375 million each of killed paratyphoid bacilli A and B and two each containing 1 000 million killed typhoid bacilli of the same strain and 750 million each of killed paratyphoid bacilli A and B 5 cc and 20 cc vials containing in each 1 cc 1 000 million killed typhoid bacilli of the same strain and 750 million each of killed paratyphoid bacilli A and B Preserved with 0.5 per cent of phenol

WYETH, INCORPORATED

Typhoid Paratyphoid Bacterial Vaccine Immunizing 1 cc vials in packages of three, one containing 500 million killed typhoid bacilli (Rawlings strain or Panama carrier strain 58 as desired) and 250 million each of killed paratyphoid bacilli A and B and two each containing 1 000 million killed typhoid bacilli of either of the same strains and 500 million each of killed paratyphoid bacilli A and B and in hospital sets of ten such units each, 5 cc 10 cc 20 cc and 50 cc vials containing in each 1 cc 1 000 million killed typhoid bacilli of either of the same strains and 500 million each of killed paratyphoid bacilli A and B Preserved with 0.25 per cent of cresol

Bacterial Vaccines Mixed

These contain more than one species of bacteria

Actions and Uses—The employment of bacterial vaccines should be based either on the discovery of the causative microorganism by careful bacteriologic examination of the patient under treatment or on well established clinical knowledge which has shown the disease present to be regularly due to the activity of a definite germ. As a rule one organism plays the predominant role and the destruction of the causative agent will effect a cure. In some cases however it has been found that two or more organisms are associated in producing the diseased condition. In such cases a vaccine containing all the known causative antigens has been thought to be indicated. When this etiologic association has been determined by actual bacteriologic examination a mixture of two autogenous vaccines or two corresponding stock vaccines may have a logical basis. If the bacteriologic examination is omitted the mixture rests on a purely hypothetical assumption and the method becomes wholly irrational.

Toxoid-Vaccine Mixtures

STAPHYLOCOCCUS TOXOID-VACCINE MIXTURE—A mixture containing in each cubic centimeter 2 000 million killed *Staphylococcus aureus* and the staphylococcus toxoid derived from 1000 necrotizing doses of toxin

Actions and Uses—Staphylococcus toxoid vaccine mixture is used in infections of recognized staphylococcic etiology. Such a mixture has been offered to neutralize the toxin and lysis of the invading organism. Local reactions may follow injection.

Dosage—Ten doses the first dose being 0.1 cc (200 million Staphylococcus aureus staphylococcus toxoid 100 necrotizing doses) the tenth 1.0 cc. Each dose is increased by 0.1 cc. The agent is given subcutaneously at weekly intervals.

THE NATIONAL DRUG CO.

Vatox Staphylococcus Toxoid Vaccine 6 cc vials. Preserved with merthiolate 1:10,000.

Diagnostic Agents

TOXINS FOR IMMUNITY TESTS

DIPHTHERIA TOXIN FOR THE SCHICK TEST

Schick Test Toxin—A sterile solution of the toxic products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*). It complies with the requirements of the National Institute of Health of the United States Public Health Service.
U S P

For description and standards see the U S Pharmacopeia under Diphtheria Toxin For The Schick Test.

Actions and Uses—This test is intended to determine those persons who are immune to diphtheria. In nonimmune persons a circumscribed area of redness and infiltration from 1 to 2 cm. in diameter develops at the site following injection of 0.1 cc of the Schick test material representing $\frac{1}{50}$ M. L. D. of diphtheria toxin. The reaction occurs in from twenty-four to forty-eight hours and is at its height in from forty-eight to seventy-two hours. It remains for from six to twelve days, is followed by slight scaling and leaves a brownish pigmented spot. In some persons a pseudoreaction may occur which may be differentiated by its earlier appearance and disappearance and the fact that it is less circumscribed and is not followed by pigmentation.

Diphtheria toxin diluted for use with isotonic solution of sodium chloride soon loses potency. Dilution of the material should be made only on the day of test. Diphtheria toxin diluted with peptone solution and certain other agents, especially boric acid and borates or human albumin is apparently quite stable.

Dosage—Intracutaneous for determining susceptibility (Schick Test) 0.1 cc of the dilution representing one fiftieth of the minimum lethal dose. **U S P**

CUTLER LABORATORIES

Diphtheria Toxin for the Schick Test Vial containing a sufficient volume of diphtheria toxin to provide approximately 50 test doses after dilution packaged with a vial containing sterile isotonic solution of sodium chloride.

Diphtheria Toxin for the Schick Test, Diluted 1 cc vial containing sufficient diluted toxin for 10 tests Preserved with 0.5 per cent phenol

LEDERLE LABORATORIES, INC

Diphtheria Toxin for Schick Test in Peptone Solution 0.1 cc syringes and 5 cc vials containing sufficient diluted toxin for 1 and 50 tests respectively, also in the form of heat treated peptone-diluted toxin in packages of one syringe and of one vial containing sufficient material for 1 and 10 control tests respectively

ELI LILLY AND COMPANY

Diphtheria Toxin for Schick Test, Diluted 1 cc and 10 cc vials containing sufficient diluted toxin for 10 and 100 tests respectively, in isotonic solution of sodium chloride containing 0.1 per cent gelatin

NATIONAL DRUG COMPANY

Diphtheria Toxin for Schick Test, Diluted 1 cc, 5 cc and 10 cc ampul vials containing sufficient diluted toxin for 10, 50 and 100 tests respectively Preserved with merthiolate 1:10,000

PARKE, DAVIS & COMPANY

Diphtheria Toxin Diluted for Schick Test 1 cc, 5 cc and 10 cc vials containing sufficient diluted toxin for 10, 50 and 100 tests respectively also supplied in the form of heat treated diluted toxin for control tests

PITMAN MOORE COMPANY

Diphtheria Toxin for the Schick Test 1 cc vial containing sufficient diluted toxin for 10 tests Preserved with 0.5 per cent phenol

SHARP & DOHME, INC

Diphtheria Toxin for Schick Test, Diluted 1 cc, 5 cc and 10 cc vials containing sufficient diluted toxin for 10, 50 and 100 tests respectively also supplied in the form of heat treated diluted toxin in 5 cc vial containing sufficient material for 50 control tests

E R SQUIBB & SONS

Diphtheria Toxin for the Schick Test (In Peptone Solution) 1 cc and 10 cc vials containing sufficient diluted toxin for 10 and 100 tests respectively preserved with 0.5 per cent of phenol

WYETH, INCORPORATED

Diphtheria Schick Test Toxin Diluted 1 cc 25 cc and 5 cc vials containing sufficient diluted toxin for 10 25 and 50 tests respectively, also in the form of heat treated diluted toxin in vials containing sufficient material for 10 25 and 50 control tests respectively

SCARLET FEVER STREPTOCOCCUS TOXIN FOR DICK TEST—For definition see this title under Bacterial Toxins

Actions and Uses—The toxin of the hemolytic streptococcus of scarlet fever is used for determination of susceptibility to against scarlet fever. The on human beings and diluted st dose

The test dose is injected intracutaneously on the forearm and the degree of sus
twenty two to twenty

or more in diameter

tion while a smaller

Reactions which hav

at the end of twenty four hours are regarded as negative

Positive reactions fade rapidly and have usually disappeared at the end of from forty-eight to seventy two hours

Scarlet fever streptococcus toxin diluted for use will retain its potency for at least two months at room temperature

LEDERLE LABORATORIES INC

Scarlet Fever Streptococcus Toxin for the Dick Test 20 cc and 110 cc vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests respectively Preserved with 0.4 per cent phenol

NATIONAL DRUG COMPANY

Scarlet Fever Streptococcus Toxin for the Dick Test 2 cc and 11 cc vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests respectively Preserved with 0.4 per cent phenol

PARKE DAVIS & COMPANY

Scarlet Fever Streptococcus Toxin for Dick Test 2 cc vials containing sufficient diluted toxin for withdrawal to perform 5 tests

Scarlet Fever Streptococcus Toxin for Dick Test
10 cc vial containing sufficient diluted toxin for withdrawal to perform 50 tests

SHARP & DOHME, INC

Scarlet Fever Streptococcus Toxin for the Dick Test
2 cc ampuls containing sufficient diluted toxin for withdrawal to perform 5 tests

Scarlet Fever Streptococcus Toxin for the Dick Test
11 cc vial containing sufficient diluted toxin for withdrawal to perform 50 tests

E R SQUINN & SONS

Scarlet Fever Streptococcus Toxin for Dick Test
2 cc. and 11 cc. vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests respectively Preserved with 0.3 per cent of phenol

U S STANDARD PRODUCTS CO

Scarlet Fever Streptococcus Toxin for the Dick Test
2 cc ampuls containing sufficient diluted toxin for withdrawal to perform 5 tests and 11 cc vial ampuls containing sufficient diluted toxin for withdrawal to perform 50 tests Preserved with phenol 0.4 per cent

WYETH INCORPORATED

Scarlet Fever Streptococcus Toxin for the Dick Test
2 cc and 10 cc. vials containing sufficient diluted toxin for withdrawal to perform five and fifty tests respectively Preserved with 0.4 per cent phenol

SCARLET FEVER STREPTOCOCCUS ANTI TOXIN FOR SCHULTZ CHARLTON TEST—(For definition and descriptions of scarlet fever streptococcus anti toxin see this title under Antitoxins)

Actions and Uses—The antitoxic serum of the hemolytic streptococcus of scarlet fever which is used to produce temporary passive immunity and in the treatment of the disease is also used in the performance of a skin test to differentiate the rash of scarlet fever from eruptions due to other causes. When doubt exists as to the nature of the eruption in cases where a diagnosis of scarlet fever cannot otherwise be ruled out a small dose of not more than 0.2 cc (containing 2000 to 5000 original neutralizing units) of the antitoxin is injected intracutaneously in the exanthematous area for the test. A positive reaction is known as the Schultz Charlton phenomenon and consists in the more or less complete disappearance of the rash over an area of 2 cm or more in diameter at the site of injection within four to twenty four hours. This reaction is of significance

because only scarlet fever immune serum is specific against the toxin responsible for the rash in this disease. Fading or blanching of the rash at the site of injection of scarlet fever antitoxin is therefore, the result of local neutralization of the toxin of this disease. The reaction usually remains evident for several days or until the rash in general has begun to fade.

NATIONAL DRUG COMPANY

Scarlet Fever Streptococcus Antitoxin, Refined and Concentrated 1 cc vial containing sufficient antitoxin for five tests

PARKE, DAVIS & COMPANY

Scarlet Fever Streptococcus Antitoxin 1 cc vial containing sufficient antitoxin for five tests

TRICHINELLA EXTRACT—*Trichinella* extract is diluted saline extraction of clean *Trichinella* larvae prepared by artificial digestion of muscles of heavily infested experimental animals. The extract is adjusted to neutrality and sterilized by filtration.

Actions and Uses—*Trichinella* extract is used for making the intradermal diagnostic skin test in the diagnosis of trichinosis. An immediate or delayed type of positive reaction may result from the intradermal injection of 0.1 cc of the diluted antigen depending on the duration of the illness.

ELI LILLY AND COMPANY

Trichinella Extract Two 1 cc vials, one vial of *Trichinella* Extract 1:10,000 dilution in isotonic solution of sodium chloride, and one control vial of isotonic solution of sodium chloride used as extracting fluid. Both extract and control solution contain Merthiolate (Sodium Ethyl Mercuri Thio salicylate Lilly) 1:20,000 as a preservative.

TUBERCULINS—Many different methods have been used to prepare from the tubercle bacillus (*Mycobacterium tuberculosis*) substances which might be used in the diagnosis or treatment of tuberculosis. These have been in general called tuberculins and a few of the more prominent are enumerated here. For diagnosis either Koch's old tuberculin or a preparation from the filtrate of a synthetic nonprotein culture medium in which tubercle bacilli have been grown is usually employed. For treatment each tuberculin has its advocates but it is doubtful whether there is any essential difference in the action of the various forms. The strength varies however not only in tuberculins prepared by different methods but also in different batches.

prepared in exactly the same manner. A tuberculin designated Purified Protein Derivative has been prepared within the last few years and is now extensively employed.

Tuberculin has a wide use in the diagnosis of tuberculous infection. A positive reaction to tuberculin indicates that infection with the tubercle bacillus has occurred. The great majority of people who have been infected by tubercle bacilli react to tuberculin so that the tuberculin test is a valuable procedure in epidemiological investigations. However, a small proportion of people who have been infected do not react, and this fact must be taken into account in epidemiological studies. Patients with far advanced or rapidly progressive disease may not react, and on the other hand persons who have made a complete recovery from slight tuberculous infection may also be negative to tuberculin, also in the presence of febrile disease as in measles the capacity to react may be temporarily abolished.

Tuberculin has its widest usage at the present time in tuberculosis case finding. Its use is based on the assumption that practically all persons with clinical tuberculosis react to tuberculin. The tuberculin test is cheaper than roentgenological examination with standard size film and therefore if it is negative is a measure of economy, obviating the necessity of the most costly examination.

In cases of pulmonary or glandular disease of obscure etiology particularly in children the tuberculin test is of value for in such cases within the limitations set in the preceding paragraph failure to react to tuberculin excludes tuberculosis in the diagnosis.

In recent years the use of tuberculin in the treatment of tuberculosis has declined greatly. At present tuberculin is more commonly employed in the treatment of nonpulmonary than pulmonary tuberculosis although individual practice varies and a few physicians use this form of therapy routinely in pulmonary cases. Treatment is generally carried out by beginning with a small dose, not large enough to cause any constitutional disturbance, and increasing the dosage gradually in injections at intervals of a few days or weeks. Ordinarily old tuberculin is employed but the other preparations listed in the following paragraphs are used occasionally. The tuberculin treatment is not a true form of immunization. The basis for treatment lies first in the fact that the substance properly used, causes a mild focal reaction at the site of infection leading gradually to fibrosis and second in the fact that frequently repeated injection gradually desensitizes the body temporarily. Desensitization to tuberculin is believed to prevent destructive reactions when spread of tubercle bacilli occurs in the body.

Danger from Tuberculin—The early history of the therapeutic use of tuberculin is full of instances showing that it may be a dangerous substance. The great risk lies in the chance of a severe reaction and every precaution should be taken in treatment not to underestimate the patient's susceptibility to the

tuberculin This susceptibility varies enormously in different individuals and at different stages of the treatment entirely out of relation to the progress of the disease. The use of tuberculin in treatment therefore requires special knowledge and experience. The doses ordinarily used in diagnosis rarely lead to constitutional reaction.

PITMAN MOORE COMPANY

Tuberculin (Diagnostic) Packages containing three 1 cc. diaphragm stoppered vials of tuberculin one of each dilution 1:100, 1:1,000 and 1:10,000. Preserved with 0.5 per cent phenol.

PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN—This type of tuberculin is made from a preparation analogous to old tuberculin differing chiefly in that a non-protein medium is used instead of glycerol bouillon for the growth of tubercle bacilli. The culture fluid and bacilli after ten weeks of growth are heated as in the preparation of old tuberculin and the bacilli are filtered off and the filtrate concentrated. After this all constituents of the original medium and all diffusible products of bacillary growth are removed by ultrafiltration, a method of pressure dialysis and what is believed to be the active principle of tuberculin is precipitated by ammonium sulfate at pH 7.0 or trichloroacetic acid. The precipitate is reprecipitated, washed and dried. It is dispensed in solid stable form permitting the preparation of solutions of definite concentration.

The method of administration is the Mantoux test described under the heading Old Tuberculin. Intracutaneous injection is made as with old tuberculin but instead of the doses given for old tuberculin standard doses of 0.00002 mg. and 0.005 mg. of purified protein derivative of tuberculin are employed. The method of reading reactions is the same as that given in the section on old tuberculin.

PANKE, DAVIS & COMPANY

Tablets Tuberculin Purified Protein Derivative (First Strength) Packages containing 2 vials (5 tests each) and 1 cc. vial of sterile diluent and packages containing 10 tablets (100 tests) with 10 cc. vial of diluent.

Tablets Tuberculin Purified Protein Derivative (Second Strength) Packages containing 2 vials (5 tests each) and 1 cc. of sterile diluent and packages containing 10 tablets (100 tests) with 10 cc. vial of diluent.

Tablets Tuberculin Purified Protein Derivative (First and Second Strength) Packages for individual testing containing 2 vials, 1 tablet each of first strength and 2 vials, 1 tablet each of second strength with a 5 cc. vial of sterile diluent.

OLD TUBERCULIN — Tuberculin Koch — Concentrated liquid culture medium of the soluble products of growth of the tubercle bacillus (*Mycobacterium tuberculosis*) and should contain about 50 per cent of glycerin. It complies with the requirements of the National Institute of Health of the United States Public Health Service U S P

For description and standards see the U S Pharmacopeia under Old Tuberculin

Actions and Uses — For diagnosis old tuberculin is used most commonly by intracutaneous injection (Mantoux test) or cutaneously by application to a scarified spot on the skin (von Pirquet test). It may also be used in the form of an ointment or paste applied directly (Moro test) or through the medium of an absorbent material or patch (patch test). The latter method has gained in popularity in recent years. Inflammation at the site of application is evidence that at some time the patient has been infected with tubercle bacilli. In such cases the reaction is called positive.

The intracutaneous (Mantoux) test is most commonly employed. Concentrated old tuberculin is diluted under sterile precautions so that 0.1 cc (the quantity to be injected) will contain 0.01 cmm of old tuberculin (commonly but erroneously called 0.01 mg). Dilution of the tuberculin should be made on the day of test.

The diluted material should be injected intracutaneously into the skin of the flexor surface of the forearm. A 1 cc tuberculin syringe and a sharp 26 gauge one half inch needle are used.

The reactions are read 48 to 72 hours after injection. In ordinary practice if the reaction is negative following a dose of 0.01 cmm a second dose of 10 cmm is injected into the opposite forearm. Occasionally for extra precaution an intermediate dose of 0.1 cmm is employed and sometimes this dose only is used. The latter practice saves time but occasionally moderately severe reactions may occur and it is generally recognized that a number of persons who would be positive to 10 cmm do not react to 0.1 cmm. In the absence of a reaction following the last dose of tuberculin the patient is regarded as negative. The reaction consists in a papule of edema 5 mm in diameter with a surrounding zone of redness at the point of the tuberculin injection. If there is no edema or induration the reaction should be considered negative. This reaction ordinarily reaches its height in forty eight hours.

For treatment from one one hundred millionth (0.00000001) to one millionth (0.000001) cc may be used as the initial dose and not more than two doses a week should be given.

The patch test a modification of the Moro percutaneous test may be used for infants and children wherever there is objection to the use of the needle. Filter paper saturated with tuberculin and dried is affixed in contact with the skin after

cleansing with acetone or ether. The patch test must be kept dry. The test is read after 48 hours. A positive reaction consists of a sharply circumscribed, reddened and infiltrated area with follicular elevations. The patch test is equivalent to the first strength (0.01 emm) of old tuberculin intracutaneously. Therefore, if negative a second test with 0.1 emm or 1.0 emm of old tuberculin may be performed by intracutaneous injection.

CUTTER LABORATORIES

Tuberculin for the Cutaneous Reaction (Pirquet's)
Capillary tubes in packages of three. Preserved with 0.5 per cent phenol.

Tuberculin Old (Tuberculin O. T.) 1 cc vial of concentrated tuberculin (human type) also supplied in serial dilutions ranging from 0.01 to 100 mg per cubic centimeter. Preserved with 0.5 per cent phenol.

IEDERLE LABORATORIES INC

Intracutaneous Tuberculin for the Mantoux Test
Vial containing old tuberculin supplied with a vial containing isotonic solution of sodium chloride sufficient to make 1 cc containing 1 mg of tuberculin. Preserved with 50 per cent glycerin.

Tuberculin Old (Koeh's) 1 cc container of tuberculin.

Tuberculin Patch Test (Vollmer) Cellophane wrapped assembled adhesive strip having two test squares and one control square each of filter paper saturated with concentrated old tuberculin and concentrated uninoculated broth respectively.

U. S. patent 2,190,745 (Feb. 20, 1940 exp. res. 1957).

ELI LILLY AND COMPANY

Old Tuberculin, Human Strain Concentrated 1 cc vials containing 1 Gm of tuberculin or containing a stated amount of concentrated tuberculin for making dilutions containing from 0.001 mg to 100 mg per cubic centimeter each packaged with a vial of physiological solution of sodium chloride for making serial dilutions.

Pirquet Test Capillary tubes each containing old tuberculin sufficient for one test in packages of three.

NATIONAL DRUG COMPANY

Tuberculin Intracutaneous for Mantoux Test 1 cc ampuls of a 1:1000 dilution of old tuberculin sufficient for ten initial tests and of a 1:100 dilution sufficient for the same number of secondary tests in packages of one ampul containing the first dilution of one ampul containing the second dilution with an accompanying vial of glycerin bouillon for the same

number of control tests and of two ampûls each containing the first and second dilutions respectively Preserved with 0.5 per cent phenol

Tuberculin Old (Human) 1 cc vial containing 1 Gm of tuberculin Koch 10 cc ampul vials in packages of five serial dilutions containing in each 2 minims 0.001 mg 0.01 mg 0.1 mg 1 mg and 20 mg respectively of old tuberculin Preserved with 0.5 per cent phenol

PARKE DAVIS & COMPANY

Tuberculin Old (Koch) 1 cc vials preserved with 50 per cent of glycerin

Tuberculin Old and Control for the Pirquet Test Sealed tubes in packages of three each tube containing tuberculin sufficient for one test accompanied by three tubes of bouillon for control preserved with 50 per cent of glycerin

Tuberculin for the Mantoux Test 10 cc vial containing 0.01 cc of old tuberculin (Koch) packaged with a 10 cc vial of diluent A filtrate from bouillon cultures from both human and bovine preserved with 50 per cent of glycerin

WYETH INCORPORATED

Intracutaneous Tuberculin for the Mantoux Test 1 cc vial containing diluted tuberculin sufficient for ten tests Each 0.1 cc represents 0.1 mg of tuberculin

Original Tuberculin O T 1 cc and 3 cc vials

Tuberculin Solution for the Pirquet Cutaneous Diagnostic Test Capillary tubes each containing sufficient old tuberculin for one test in packages of 1 5 and 10 tubes

Undiluted Tuberculin Old Syringe containing concentrated old tuberculin supplied with three vials of diluent for the preparation of dilutions 1:100 (1 cc of which represents 10 mg of tuberculin) 1:1000 (1 cc of which represents 1 mg of tuberculin) and 1:10000 (1 cc of which represents 0.1 mg of tuberculin)

NEW TUBERCULIN B E—Tuberculinum Novum
B E—Bazillenemulsion Koch—Bacilli Emulsion—Bacilli emulsion is practically a bacterial vaccine It is made by suspending one part of pulverized tubercle bacilli *Mycobacterium tuberculosis* in 100 parts of distilled water and 100 parts of glycerin One cc thus corresponds to 5 mg of tubercle bacilli

It is a white, fairly permanent emulsion but should be shaken thoroughly before making dilutions New tuberculin B E. is occasionally used in the treatment of tuberculosis

NEW TUBERCULIN B E DRIED—*Tuberculinum Novum B E Siccum*—A solution of this is practically a bacterial vaccine. The *Tab. B E* is dried ground mixer. The diluent is adj. will represent the *Tab. B E* about 1 of new tuberculin B E dried per cc.

NEW TUBERCULIN T R—*Tuberculinum Novum T R*—*Tuberkelbacillin Rest Koch*—*Tuberculin Residue*—*Tuberculin Ruckstand*—This is made from living dried tubercle bacilli *Mycobacterium tuberculosis* by grinding to complete disintegration. The water insoluble material is suspended in glycerin and water. The final product contains the residue of 10 mg of dried tubercle bacilli in each cc of fluid. New tuberculin is an uncolored slightly opalescent liquid. It is used occasionally in the treatment of tuberculosis.

NEW TUBERCULIN T R DRIED—*Tuberculinum Novum T R Siccum*—*Tuberculin Residue (Dried)*—The mass culture of *Mycobacterium tuberculosis* is repeatedly ground and washed until all water soluble material has been removed. The residue is then ground to complete disintegration, dried, mixed with a suitable base and made into tablets. Each tablet represents a definite amount of dry tubercle bacilli.

TUBERCULIN DENYS — *Tuberculinum Denys* — *Tuberculine Bouillon Filtré*—*Bouillon Filtrate Tuberculin*—This is prepared like old tuberculin without the prolonged heating and concentration that is it is simply a glycerin broth culture of the tubercle bacillus *Mycobacterium tuberculosis* passed through a porcelain filter. It contains all the soluble products of the growth of the tubercle bacillus.

CHAPTER XXIV

VITAMINS AND VITAMIN PREPARATIONS FOR PROPHYLACTIC AND THERA- PEUTIC USE VITAMINS

The investigations of nutrition that have been initiated since the second decade of the present century have afforded an entirely new outlook upon many disorders some of which have long been suspected to be of dietary origin. This is due to the scientific demonstration that factors other than proteins, carbohydrates, fats and minerals are essential for the preservation of bodily well being and physiologic function. These factors are designated at the present time as vitamins.

The absence of any one of the vitamins from a diet which is satisfactory in other respects leads to the development of a typical syndrome which is called a deficiency disease. These diseases may be as striking in their manifestations as are the direct result of underfeeding (caloric deficiency) or deprivation of essential inorganic elements such as iodine, iron, calcium or phosphorus. A striking illustration of a deficiency disease is presented by scurvy. This can be entirely averted or effectively cured by the inclusion of foods which contain vitamin C (ascorbic acid) in the diet. It has been clearly established by convincing experiments that the prophylactic or remedial agent—the antiscorbutic substance—is a definite chemical entity having the composition $C_6H_8O_6$. The vitamin is present in many articles used as food such as fresh vegetables and fruits yet entirely lacking in others such as the common cereals and grains. Ascorbic acid is readily destroyed by heat under certain conditions notably in an alkaline medium and in the presence of oxygen. However, foods can be processed without serious loss of ascorbic acid if precautions are taken to exclude air and if the reaction of the food is not unfavorable for the preservation of the vitamin.

The foregoing illustration will suffice to indicate the characteristics of a vitamin—a substance essential for maintenance of normal metabolic functions not identical with the more familiar nutrients not synthesized in the human body in normally adequate amounts and therefore to be furnished by an exogenous supply sometimes more labile than the foodstuffs proper and hence subject to deterioration and distributed variously among the edible parts of animals and plants. More than twenty naturally-occurring compounds having vitamin activity have been isolated and identified. There are now available many commercial preparations in pure synthetic form having the same physiologic properties as the naturally occurring compounds.

For convenience etc, have arisen thalnia have been certain- and D keroph mental
 certainty to the lack of specific vitamins, the protective or curative substances are accordingly sometimes spoken of as the antiscorbutic vitamin (C), the antineuritic vitamin (B_1), the antirachitic vitamin (D), the the antixerophthalmic vitamin
 physiology of the vitamins c.
 textbooks on physiological chemistry and nutrition. The problems raised thereby are the subject of active discussion and extensive investigation so that with respect to many features only tentative conclusions should be announced at this time.

Chemical, physical and microbiologic methods are now in general use for the determination of vitamins in pharmaceutical products but biologic assays must be used for vitamin D and for checking other determinations. To facilitate such assays and to make uniform the expression of vitamin content the Health Organization of the League of Nations has sponsored the preparation and distribution of standards for vitamins A, B_1 , C and D. The International unit for each of these vitamins is defined in terms of the biological activity of a specific quantity of the respective standard. The U S P units for vitamins A, B_1 , C and D are identical in value. The United States Pharmacopoeia pro-
 totype standards for these refer-
 ence standards for riboflavin and nicotinic acid.

The Council has decided that when practicable vitamin content should be stated in milligrams in preference to micrograms or units. This action was prompted by recognition that confusing practices have grown up in the industry concerning representations for the vitamin content of products. The vitamin content of some products has therefore been expressed in micrograms even though the term is wholly unfamiliar to the laity. As a result of this the purchaser may be led to believe that a product has a higher vitamin content when so represented than if units or milligrams were used. For instance one milligram of vitamin B_1 equals 333 U S P or International units or 1000 micrograms. A very similar situation prevails with respect to riboflavin. The decision is applicable to ascorbic acid, thiamine, riboflavin, nicotinic acid and vitamin K preparations and will be applied to other vitamins for which no units have been established. Vitamin A and vitamin D content should be expressed in U S P units.

While the requirements of the infant for vitamins A, B_1 , C and D have been fairly well established we do not have as much evidence that bears directly on the adult requirements for vitamins A and D. Ordinarily there is no reason why a properly selected diet should not afford an adequate supply of the requisite vitamins. Furthermore with the exception of pellagra there is no evidence of any noteworthy prevalence

in this country of conditions in adults that might properly be ascribed to a severe deficiency of one or more vitamins. However, it must be admitted that under circumstances bringing about a highly restricted dietary regimen and leading to one-sided diets a relative shortage of some of the vitamins does at times arise. In almost all such instances the situation can be properly corrected by prescription of appropriate foods. Occasionally and particularly with infants a corrective result may be more effectively secured by the administration of products especially rich in the desired vitamin, for example cod liver oil as a dietary adjunct in the prevention or treatment of rickets, and orange juice in the relief of scurvy.

The clear indications for such specific vitamin therapy are still few in number. The chief justification for the recognition of special vitamin bearing products at present applies to unusual concentrations of the desired potent principle that they may represent or to exceptionally desirable dosage forms. Multi-vitamin preparations, particularly capsules, have come into very extensive use in recent years. In most of these preparations the proportion of vitamins present has borne no relationship to

requirements for
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for accept

that the vitamin content is
the vitamins. This subject
the Journal (119 948 July

18 1942)

GENERAL PROVISIONS AND LABELING REQUIREMENTS

Statement of Vitamin Potency—When vitamin A or vitamin D potency is expressed it must be in U. S. P. units. When the vitamin content of preparations of ascorbic acid, thiamine, riboflavin, nicotinic acid, nicotinamide, pyridoxine, menadione and similar vitamin B₆ preparations is expressed it must be in milligrams and not in micrograms, gammas or units.

Vitamin preparations which supply in the recommended daily intake not more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food Drug and Cosmetic Act must be labeled to show the proportion of the minimum daily requirements supplied in the recommended daily intake.

Vitamin preparations which supply in each unit (tablet, capsule, etc.) or in the recommended daily intake more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food Drug and Cosmetic Act will be accepted if they are advertised only to the physician. To meet the requirements of the Food Drug and Cosmetic Act with respect to adequate directions for use such preparations

must bear the statement "_____ daily, or as prescribed by the physician. This dosage is in excess of the quantity needed for prevention of _____ deficiency," or a more detailed statement of directions for use.

The above labeling requirements are exemplified in the following outline of statements which should appear on the main panel of the label:

STATEMENTS REQUIRED ON MAIN LABEL

For Preparations Supplying More Than Three Times the Minimum Daily Requirements

| | |
|---|---|
| Quantity of contents | 50 tablets |
| Common or usual name | Thiamine Hydrochloride
Tablets |
| Quantity of vitamin in tablets consumed daily | 10 milligrams |
| Adequate directions for use | Dose: One tablet daily, or as prescribed by the physician. This dosage is in excess of the quantity needed for prevention of thiamine deficiency. |
| Name and place of business | John Doe
550 Broad Street
Chicago, Illinois |

For Preparations Supplying Three Times the Minimum Daily Requirements or Less

| | |
|---|---|
| Quantity of contents | 100 tablets |
| Common or usual name | Thiamine Hydrochloride
Tablets |
| Quantity of vitamin in tablets consumed daily | 1 milligram |
| Dose | This is optional |
| Proportion of minimum daily requirement | 1 tablet will supply the minimum daily requirement for an adult |
| Name and place of business | John Doe
550 Broad Street
Chicago, Illinois |

General Allowable Claims for Vitamins

Growth—A deficiency of any food essential will undoubtedly lead to retardation of growth. This is true of each of the essential vitamins but it is equally true of each of the essential amino acids, minerals and of energy yielding compounds.

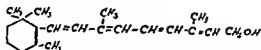
Statements conveying the impression that one vitamin is more important than other vitamin or food essential in promoting growth are therefore considered misleading and objectionable.

Infections—A person suffering from malnutrition is more susceptible to certain types of infections than the normal individual. The types of infections which may occur in malnutrition have not been shown to be more closely correlated to specific deficiencies than to the organisms to which the body may be exposed. Secondary infections are characteristic of conditions resulting from severe vitamin deficiency. Investigations have failed to show that the administration of vitamins far in excess of bodily needs makes one more resistant to diseases than the ingestion of quantities which are just sufficient to meet normal metabolic requirements.

Vitamin A

The term vitamin A has been applied to any one of several substances or to a mixture of them producing a certain demonstrable specific physiologic effect. It seems to have been definitely established that there are at least five substances which can produce to some degree this characteristic response in the animal body. These are vitamin A itself, alpha, beta and gamma carotene and cryptoxanthin. The last four of these the precursors of vitamin A are produced in the plant kingdom and ingestion of these substances by most animals results in varying degree (depending on the species of animal and the precursor fed) in the formation of a compound having the empirical formula $C_{20}H_{30}OH$ and to which no other name than vitamin A has been given. The extent to which the different precursors of vitamin A can be converted to vitamin A by different species of animals has not definitely been established. The exact function of vitamin A has not been established but the pathological picture which results from varying degrees of deficiency has been the subject of extensive investigation.

Vitamin A has the following structural formula



The claims recognized for vitamin A shall be recognized for the precursors of vitamin A only under conditions specified elsewhere for Carotene.

Acceptance of Vitamin A preparations will be limited to those containing in each capsule, tablet or average dose of fluid 25,000 U. S. P. units or less of Vitamin A.

Allowable Claims—1 Evidence for the existence of vitamin A and its role in human nutrition is based on the fact that a characteristic eye disease, usually called xerophthalmia, results from a deficiency of this vitamin.

2 It is generally agreed that the first symptom or at least one of the first clinical symptoms of vitamin A deficiency is night blindness or nyctalopia. For this type of night blindness vitamin A is a specific. Cases of nyctalopia exist which do not respond to treatment with vitamin A. These may be due to congenital defects or to other diseases than avitaminosis A. In view of present knowledge the claim is not acceptable that the administration of vitamin A to drivers of automobiles will diminish the chance of accident from driving at night.

3 Vitamin A is reported to be effective in the treatment of certain types of hyperkeratosis of the skin of persons suffering from severe deficiency of vitamin A.

4 Vitamin A in excess of normal requirements has not been shown to be of value in the prevention of colds, influenza and such infections.

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The Vitamin B Complex

The term Vitamin B Complex is applied to a group of substances which have been shown to be constituents of what was formerly called vitamin B. Intensive investigations have produced an ever changing picture of the constituents which comprise the complex. At this writing seven compounds recognized as members of the vitamin B complex have been identified and are being manufactured by synthetic processes. They are:

Thiamine (vitamin B₁) or Thiamine Hydrochloride (vitamin B₁ hydrochloride) the antiberiberi vitamin which prevents beriberi in man and polyneuritis in animals. See following section on Thiamine for further discussion.

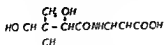
Riboflavin, a component of an oxidation reduction system of living cells. The only name suggested for the syndrome following a deficiency of this vitamin is ariboflavinosis. See following section on Riboflavin for further discussion.

Nicotinic Acid (amide) (P.P. factor) a nutritional factor effective in the treatment of human pellagra. See following section on Nicotinic Acid and Nicotinic Acid Amide for further discussion.

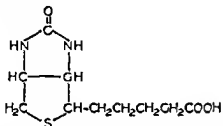
Pyridoxine (Vitamin B₆) or Pyridoxine Hydrochloride (vitamin B₆ hydrochloride) a factor for the prevention of a nutritional dermatosis in rats. There is yet no satisfactory evidence relating to its therapeutic value for man.

Pantothenic Acid, a factor for the prevention of a nutritional dermatosis in chicks and necessary for the growth of rats. Its value in human nutrition has not been demonstrated.

Pantothenic acid has the following structural formula



Biotin has the following structural formula



This compound combines with a protein like substance in raw egg white called 'avidin'. In suitable diets containing large proportions of raw egg white the rat or chick develops characteristic skin lesions and growth is retarded. These symptoms can be prevented by ingestion of biotin. The practical significance of these observations is not established because there is evidence that sufficient quantities of biotin for metabolic requirements may be synthesized in the intestinal tract.

Vitamin Bc" 'norite eluate factor' and 'folic acid' are names applied to what appear to be very similar but probably not identical compounds occurring in foods that are specific in preventing a type of anemia in the growing chick. These compounds have also been found to be effective in the cure of blood dyscrasias produced in the rat by the feeding of large amounts of some of the sulfonamide drugs. A synthetic folic acid has recently been made available for investigational use but the chemical structure of the compound has not been revealed. There are reports of the use of this synthetic compound both orally and parenterally in the treatment of pernicious anemia, macrocytic anemia of sprue and nutritional macrocytic anemia with favorable results. The period of observation has not been of sufficient duration to permit adequate evaluation of this treatment but it is now apparent that folic acid is an important member of the vitamin B complex.

In addition to these seven compounds there are other factors that have been shown to be essential nutrients for a few species of experimental animals. None of these has been shown to have any importance in human nutrition.

Thiamine

The name 'Thiamin' for vitamin B₁ was proposed by Dr R R Williams who elucidated the structure of the compound. This name and "Thiamine Chloride" for the chloride hydrochloride of the vitamin have been given acceptance by

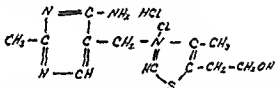
When vitamin

United States

'Thiamine Hydrochloride' this designation seems to be more in conformity with systematic nomenclature of organic compounds and the Council has voted to recognize that name. Where no reference is made to a specific compound the Council uses the term 'Thiamine' as being synonymous with vitamin B₁.

This vitamin is recognized as being of fundamental importance in connection with the disease beriberi. The pure compound was first isolated in 1927. Since that time its chemical constitution has been established and it is now being manufactured synthetically. It is usually prepared as the hydrochloride and then has the formula C₁₂H₁₇ON₄S Cl HCl.

Thiamine hydrochloride has the following structural formula



The International Conference on Vitamin Standardization has adopted crystalline vitamin B₁ hydrochloride as the standard for this vitamin and defined the unit as the biological activity of three micrograms of this standard.

Allowable Claims—1 Thiamine is of value in correcting and preventing beriberi.

The general opinion of the students of beriberi is that this disease with its nervous and cardiovascular manifestation is due primarily to an insufficient supply of thiamine. It is probable that in the majority of instances of human beriberi there are also deficiencies of food constituents other than thiamine. There are conditions which probably could be designated as 'latent beriberi', it does not seem wise at this time to attempt the formulation of a definite statement covering such conditions other than that presented in Item 5.

2 Thiamine may be cited as of value in correcting and preventing anorexia of dietary origin in certain cases.

There are many causes of anorexia, some referable to infections and the reactions thereto, others to organic disorders and still others related to faulty diet. Where there is no rather obvious cause of anorexia in question other than a possible

dietary one it is permissible to claim that thiamine may be of therapeutic value when the condition to be treated is due to a deficiency of that vitamin

3 The administration of thiamine in excess of that present in the ordinary diet may be advantageous when there are specific conditions indicating interference with proper assimilation of the vitamins

The present status of research on the clinical use of thiamine for specific diseases other than beriberi and for infant feeding is such that *definite* claims for therapeutic value in relation to such diseases cannot be recognized. Its use may be indicated however, in such restricted conditions as pernicious vomiting of pregnancy, tube feedings through a jejunal fistula and the like because the above permitted statement applies to such conditions and gives an intelligent basis for such therapy

4 While it has not been established that thiamine deficiency is the sole cause of conditions described as alcoholic neuritis, the neuritis of pregnancy and the neuritis of pellagra, there is some definite evidence of the value of this vitamin in the treatment of these conditions. Vague representations with respect to the value of thiamine in the treatment of other types of neuritis are not permissible

5 Thiamine deficiency in animals is associated with dysfunctions of the heart and of the vascular system. Thiamine is effective in reestablishing the normal function of the cardiovascular system if the dysfunction was caused by thiamine deficiency. Evidence is lacking that thiamine is effective in any other type of heart disease. At times organic heart disease and beriberi heart coexist. Administration of thiamine is justified in these patients

6 It appears that there is an increased requirement for thiamine when there is greatly augmented metabolism such as occurs in febrile conditions, hyperthyroidism or vigorous muscular activity

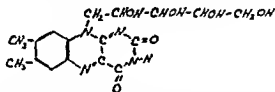
7 Claims for concentrates containing thiamine offered for clinical use should state the potency of this agent in terms of milligrams. The term concentrate or a synonym will not be recognized if the product does not exceed a potency of 0.075 mg per gram (or per cubic centimeter) or if it is a natural product which may have been subjected to a process of dehydration

Riboflavin

Riboflavin, the empirical formula of which is $C_{17}H_{20}N_4O_6$, was formerly known as Vitamin G, Vitamin B₂, or Lactoflavin. The chemical nature of the vitamin was established in 1935. In 1936 the Council voted to accept riboflavin for purposes of standardization and clinical experimentation. Since that time

sufficient evidence has been accumulated to justify the acceptance of the product as a therapeutic agent. The vitamin is equally effective whether administered orally or parenterally.

Riboflavin has the following structural formula



Allowable Claims—1 Riboflavin is recognized as a specific in the treatment of certain characteristic lesions of the tongue, the lips, and the face. The symptoms may be described briefly as follows. A typical glossitis may often be observed before other signs of riboflavin deficiency are present. In contrast to the glossitis of pellagra, the tongue is clean, the papillae are flattened, and the color is scarlet, as if the tongue had been macerated in a solution of potassium permanganate. Frequent labial fissures are observed at the corners of the mouth. The above symptoms disappear with the administration of adequate amounts of riboflavin.

2 Riboflavin deficiency is responsible for certain ocular manifestations characterized by itching, burning and a sensation of roughness of the eyes (keratitis), accompanied by mild photophobia. The anatomical changes may vary from a superficial invasion of the cornea by capillaries to an extensive vascular proliferation with or without infiltration opacity, and exudate formation. These symptoms, when due to a riboflavin deficiency are relieved promptly by the administration of the vitamin.

3 It is permissible to recommend the use of riboflavin for the alleviation of symptoms of riboflavin deficiency encountered in other diseases, notably pellagra

Nicotinic Acid And Nicotinamide

Nicotinic acid ($C_6H_5O_2N$) and nicotinamide ($C_6H_5ON_2$) are of fundamental importance in the treatment of pellagra. The terms niacin and niacin amide, are now officially recognized as synonyms for these chemical names. The pure compounds have been known for many years but not until recently were they recognized as therapeutic agents. In 1938 the Council voted to accept nicotinic acid and nicotinamide 'for purposes of standardization and clinical experimentation. Sufficient evidence has now been accumulated to demonstrate the usefulness

of these drugs. Administration of relatively large doses of nicotinic acid produces a marked flushing of the face and neck. There is an unpleasant sensation but the reaction is transient and apparently harmless. This effect is not observed following the administration of nicotinamide. For parenteral use nicotinamide is the drug of choice.

Nicotinic acid has the following structural formula



Nicotinamide has the following structural formula

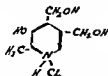


Allowable Claims—1 Nicotinic acid and nicotinamide are recognized as specifics only in the treatment of pellagra. Their administration in appropriate doses lead to the disappearance of all alimentary, dermal, and other lesions characteristic of the disease to a return to normal of the porphyrin and porphyrin like pigments of the urine, and to a profound improvement in the mental symptoms when the latter are the result of an inadequate intake of nicotinic acid and nicotinamide. These compounds are without influence upon the polyneuritis or cheilosis so frequently observed in pellagrous patients. In such cases it may be necessary to insure the presence in the diet of foods rich in vitamin B₁ or B₂ or to administer thiamine hydrochloride, riboflavin or both.

Pyridoxine

The terms 'pyridoxine' and 'pyridoxine hydrochloride' are synonymous with 'vitamin B₆' and 'vitamin B₆ hydrochloride'.

Pyridoxine hydrochloride has the following structural formula

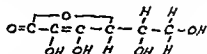


Pyridoxine has been available for too brief an interval of time and in insufficient quantities to permit its clinical evaluation. Further study of the clinical value of this compound is necessary before definite claims will be permitted. Pyridoxine is accepted to assure the availability of a preparation of satisfactory composition for investigational use.

Ascorbic Acid (Cevitamic Acid)

Suboptimal intakes of ascorbic acid result in the development of clinical and pathologic phenomena to which the descriptive term scurvy has been applied

Ascorbic acid has the following structural formula



All pure ascorbic acid that has been used in pharmaceutical products in recent years has been prepared synthetically. The International unit for ascorbic acid, which was formerly defined as the vitamin C activity of 0.1 cc of lemon juice, is now defined as the activity of 0.05 mg of ascorbic acid. This is the quantity of ascorbic acid usually found in 0.1 cc of lemon juice or orange juice.

In planning diets for infants who do not receive breast milk, and for small children, it is generally advisable to make special provision for a source of ascorbic acid such as orange juice because (a) the concentration of ascorbic acid in fresh cow's milk is only about one fourth of the concentration in mother's milk, and (b) the vitamin in most foods is very sensitive to destruction by oxidation.

Allowable Claims—1 Ascorbic acid is acceptable for the correction and prevention of scurvy. Definite claims for the therapeutic value of ascorbic acid should be permitted only in relation to scurvy until further clinical or experimental evidence has substantiated its usefulness in other states.

2 It may be permissible under certain conditions to refer to the therapeutic value of ascorbic acid in early and latent scurvy. Convincing clinical evidence has established that this state does occur. It would be well to emphasize the fact that the diagnosis rests, however, on the basis of roentgenologic evidences in the long bones, the blood level, and possibly failure to excrete an optimum amount of ascorbic acid in the urine.

3 Dental caries, pyorrhea, certain gum infections, anorexia, anemia, undernutrition and infection alone are not in themselves sufficient indications of ascorbic acid deficiency but according to experimental and clinical investigation may be concomitant signs of ascorbic acid deficiency. Therefore, it is permissible to accept the claim for the therapeutic value of ascorbic acid in these symptomatic conditions only when it is definitely stated that they are the consequences of a deficiency or suboptimal amount of ascorbic acid or when there is a pathologic interference with assimilation of the amount necessary for the preservation of health.

4 Because ascorbic acid is a dietary essential its administration in concentrated form is of value in conditions where difficulty is encountered in introducing it orally or in utilizing ordinary foods in the usual way. Ascorbic acid is accepted as an essential dietary constituent in infant feeding but it should not be accepted for use in the treatment of diseases except according to the conditions mentioned above. It is generally administered in the form of an ascorbic acid carrying juice. It may be administered parenterally in concentrated form as sodium ascorbate when persistent vomiting, diarrhea or other conditions prevent the utilization of proper amounts taken orally.

5 Dosage forms of ascorbic acid offered for clinical use must state the potency in terms of milligrams.

6 A reasonable general statement regarding allowable claims for ascorbic acid would be as follows:

An optimum amount of ascorbic acid should be supplied at all ages for its therapeutic value in preventing the development of acute or latent scurvy.

Claims for the therapeutic value of ascorbic acid may be accepted when the agent is described as a corrective measure for scurvy due to a demonstrable absence or a suboptimal quantity in the diet or in cases in which it is definitely known that there is interference with the absorption of an optimal amount.

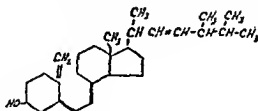
Advertising of ascorbic acid for such symptoms as failure to gain in weight or stoppage of growth, anorexia, anemia, infections, symptoms referable to the central nervous system or hemorrhagic conditions cannot be accepted unless it is definitely stated that the symptoms are referable to a demonstrable deficiency of ascorbic acid.

Ascorbic acid is easily decomposed in the presence of certain other substances; therefore care should be exercised against administering it (or orange juice) in mixtures or by any procedure which renders it ineffective.

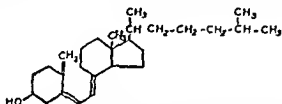
Vitamin D

The term vitamin D is applied to two or more substances which have a function in the proper utilization of calcium and phosphorus. Two forms of naturally occurring vitamin D have been isolated. One of these, vitamin D₂ or calciferol, is obtained in pure crystalline form as one of the products of the ultra violet irradiation of ergosterol. The two forms of vitamin D as well as some of the other products of irradiated ergosterol possess anti rachitic potency. They also tend to elevate the level of serum calcium, an effect which varies, however, with the different substances and which does not parallel the anti rachitic effect.

Vitamin D₂ has the following structural formula



Activated 7 dehydro cholesterol (vitamin D₃) has the following structural formula



Some reports have appeared claiming clinical improvement in chronic arthritis and in certain allergic disorders as a result of the use of massive doses of vitamin D. Critical examination of these reports reveals little to warrant the belief that the clinical effects claimed are specific. There is suggestive clinical evidence that the use of massive doses of vitamin D may cause improvement in some cases of psoriasis, but the effect is not yet well enough established to justify a claim for such use. The Council believes that further studies should be conducted but, because of the possible toxic effects of large doses of vitamin D, it is necessary that such studies should be made only in clinics where close supervision is possible. The Council also holds there is not sufficient evidence to warrant the acceptance of viosterol preparations of high potency for use in the treatment of arthritis.

Another suggested use of massive doses of vitamin D is in the treatment of refractory rickets that is occasional cases of rickets which do not respond to treatment with the usual dosages or even much larger dosages of vitamin D. In some of these cases the rickets is due to a disturbance of the acid base balance and has been successfully treated by administration of sodium bicarbonate or a sodium citrate citric acid mixture. Massive doses of vitamin D have proved effective in the control in others. The quantity of vitamin D needed may be so large that it borders on the dosages of vitamin D that are definitely toxic, and such treatment should not be undertaken without first exploring other possibilities or without careful observation for signs of toxicity. Some investigators believe it desirable to examine the urine daily for calcium casts albumin and red blood cells while the maintenance dose is being established.

Others believe less frequent examination is necessary. After the dose is established weekly examination using the Sulkowitch test for excessive excretion of calcium is sufficient. The blood should be examined weekly or oftener to avoid a rise of calcium above 12 mg per hundred cubic centimeters if the dosage exceeds 20 000 units daily for the infant or 50 000 units for a child. If anorexia or nausea should appear, the child must be brought promptly to the attention of the physician and vitamin D administration should be discontinued. When the maintenance dose has been established operative procedures to correct rachitic deformities may precipitate a temporary state of toxicity and the blood levels of calcium must be watched closely.

It is now well established that certain substances derived from activation products of ergosterol and cholesterol are effective in raising the level of serum calcium. This result is achieved in part by mobilization of calcium from the bones but also by an increased absorption of calcium only Vitamin D₂ (calciferol) and dihydrotachysterol have similar effects in comparable doses and it has not been shown that one is superior to the other in the management of hypoparathyroidism. During their use frequent determinations of serum calcium are desirable, the Sulkowitch test by which the excretion of calcium into the urine is observed is helpful and is so simple that it may be performed by the patient. Its routine use during treatment will reduce the number of necessary determinations of serum calcium.

Treatment of parathyroid insufficiency is commonly initiated with relatively large doses of the activated sterols followed by smaller maintenance doses. The management of acute parathyroid tetany may require from 2 to 8 mg of pure dihydrotachysterol which is approximately equivalent to 10 to 40 mg or 400 000 to 1 600 000 international units of vitamin D. The amount of the substances necessary for daily maintenance varies greatly in individual cases but averages between 0.6 and 1.0 mg of pure dihydrotachysterol or 3.0 to 5.0 mg (133 333 to 200 000 international units) of vitamin D.

Allowable Claims—1 Vitamin D is recognized as a specific in the treatment of infantile rickets spasmophilia (infantile tetany) and osteomalacia diseases which are manifestations of abnormal calcium and phosphorus metabolism. Vitamin D is valuable in the prevention as well as in the curative treatment of these diseases. Complications such as renal insufficiency or glandular malfunction may preclude normal response to vitamin D therapy. During acute infections especially of the gastrointestinal tract vitamin D may prove ineffective because poorly absorbed.

2 Direct exposure of the skin to ultraviolet light from the sun or from artificial sources results in the formation of vitamin D within the organism but the Council cannot recognize statements or implications that vitamin D has all beneficial effects of exposure to sunshine

3 There is clinical evidence to justify the statement that vitamin D plays an important role in tooth formation Likewise experimental evidence justifies the statement that vitamin D is a beneficial factor in preventing and arresting dental caries when the intake of calcium and phosphorus is liberal and the diet is adequate with respect to other nutrients Claims should not state or imply that vitamin D is the only important factor in caries prevention and arrest

4 Animal experimentation has shown that correction of an inadequate intake of vitamin D results in the more economical utilization of calcium and phosphorus and also that the undesirable effects of improper ratios of calcium and phosphorus in the diet can largely be overcome by normal intake of vitamin D The importance of these observations in their application to man is not entirely apparent because of the lack of adequate clinical evidence showing the availability of different forms of calcium and phosphorus but it may be stated that vitamin D has a favorable influence on calcium and phosphorus metabolism

5 Because of its effect upon the level of serum calcium vitamin D has been used in correcting the hypocalcemia of parathyroid tetany Satisfactory effects may be obtained with sufficient doses either of vitamin D₂ (calciferol) or of dihydrotachysterol a derivative of one of the products resulting from the irradiation of ergosterol When vitamin D preparations are employed for the correction of hypocalcemia patients must be under constant observation since the elevation of serum calcium above normal levels may be accompanied by serious or even fatal effects

6 Clinical evidence does not warrant the claim that massive doses of vitamin D are of benefit in chronic arthritis in allergic disorders or in psoriasis If representations are made for use of massive doses of vitamin D in the treatment of refractory rickets they must be accompanied by adequate precautions with respect to the danger of toxic effects and how they can be avoided as indicated in the paragraph immediately preceding the allowable claims for vitamin D

Vitamin E

For nearly two decades it has been known that vitamin E must be included in the diet of the rat to insure successful reproduction There are at least three naturally occurring compounds which have vitamin E activity alpha beta and gamma tocopherol There have been comparatively few clinical studies dealing with the role of vitamin E in human physiology and

they have not led to very definite conclusions. There seems to be agreement that the vitamin is of no value in the treatment of sterility. There are indications that it may be of value in the treatment of habitual abortion but further studies are necessary to clarify the picture.

Recently there has been renewed interest with respect to vitamin E owing to reports that administration of alpha tocopherol and other preparations of vitamin E have produced beneficial results in the treatment of some cases of degenerative diseases such as amyotrophic lateral sclerosis. This is not substantiated in any way by recent clinical evidence.

Vitamin K

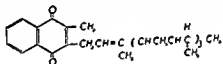
Vitamin K was discovered and named by Dam of Copenhagen in 1935 when he observed in newly hatched chicks a fatal hemorrhagic diathesis which could be cured or prevented

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at the delayed
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two naturally

occurring substances having a naphthoquinone nucleus which have similar physiologic properties and they are referred to as vitamin K₁ and vitamin K₂. Their empirical formulas are as follows



Vitamin K₁ has the following structural formula



Recently a number of naphthoquinone derivatives have been synthesized which produce a wide range of vitamin K activity some being even more potent than pure vitamin K₁ or vitamin K₂ and some of them water soluble. They have been referred to as vitamin K analogues.

The Council has recognized the term 'Menadione' for the compound 2-methyl-1,4-naphthoquinone. 'Menadione' has the following structural formula



There is now adequate demonstration that prothrombin deficiency in the blood of man may result from interference with the absorption of vitamin K. Some of the fat soluble vitamins

including vitamin K are not absorbed when the flow of bile is obstructed and synthesis of prothrombin by the liver does not occur unless vitamin K is available. Obviously it is necessary to administer bile salts with vitamin K when prothrombin deficiency is due to bile obstruction and the vitamin is given orally. While bile salts are necessary for the absorption of most of the oil preparations of vitamin K and its analogues there are now available certain water soluble materials which obviate the necessity for concurrent administration of bile salts. It has also been demonstrated that the incidence of hemorrhage in the newborn can be reduced by administering to the mother before delivery preparations having vitamin K activity. The full significance of this observation is not as yet apparent.

Allowable Claims—Vitamin K both in its crude form and in certain related naphthoquinones with analogous antihemorrhagic activity seems to have a specific effect on prothrombin deficiency occurring under certain sets of circumstances:

1 In primary dietary deficiency of vitamin K which while admittedly rare does exist

2 In obstructive jaundice in which vitamin K has proved to have an extraordinary protective effect against hemorrhagic diathesis

3 The hemorrhagic state associated with primary hepatic disease is controlled in part but not entirely by vitamin K and by the naphthoquinones with analogous activity. The difficulty seems to lie in the fact that the liver cannot utilize the material in the formation of prothrombin except to a limited degree

4 The hemorrhagic states which exist in connection with certain intestinal diseases such as ulcerative colitis sprue and celiac disease characterized by either a loss of continuity of the intestinal tract or by a disturbance of its absorptive surface are also affected in a specific manner by vitamin K.

5 In the treatment of the physiological hypoprothrombinemia of the newborn which exists during the first week of life the vitamin and its analogues seem to be a specific. It seems now fairly well established that the vitamin itself or the naphthoquinones when administered parenterally to a woman during labor in amounts as small as $\frac{1}{2}$ to 2 mg insures that the newborn infant will have a normal amount of prothrombin in the circulating blood. These doses can also be given parenterally to the newborn infant and will produce the same effect.

VITAMIN PREPARATIONS

Vitamin A Preparations

For allowable claims see preceding article. Vitamin A. Vitamin A is found in fish liver oils (which see). The provitamin A carotene gives the effects of vitamin A when ingested.

CAROTENE—Pro Vitamin A—A hydrocarbon having the empiric formula $C_{40}H_{56}$ which occurs in three isomeric forms referred to respectively as alpha beta and gamma carotene. The alpha form is optically active and the others are not. The beta form appears to predominate in nature and the gamma is found in the smallest quantities but usually a mixture of the different forms occurs. The crystals are readily oxidized. They should be kept in a vacuum or in an inert gas in the dark at a low temperature. The International unit for vitamin A adopted at the Second International Conference on Vitamin Standardization 1934 is defined as the vitamin A activity of 0.6 microgram of beta carotene. There is considerable scientific evidence indicating that alpha and gamma carotene have one half the vitamin A activity of beta carotene. The Council has reached the following decision with respect to the use of the term Pro vitamin A as a synonym for carotene (1) that the term A Pro vitamin A be regarded as a synonym for alpha beta or gamma carotene or for cryptoxanthin and that the synonym Pro vitamin A be adopted and used in New and Nonofficial Remedies for any combination of two or more of these and (2) that when this synonym is used on the label of any accepted product it appear in brackets after the Council name with a statement of the vitamin A potency of the product.

Actions and Uses—It appears that at least a portion of the carotene ingested is converted in the liver into vitamin A. Carotene therefore has actions similar to those of vitamin A. As carotene may be a mixture of the alpha beta and gamma forms its relative efficiency may vary according to the ratio of these components. Evidence is not available on which to base the exact conversion factor of carotene in terms of clinical vitamin A effect. Much depends on the conditions for absorption of pigments. The absorption of carotene and to a lesser degree that of vitamin A is decreased in steatorrhea and diarrhea both acute and chronic. Liquid petrolatum being a good solvent for carotene prevents its absorption and should not be administered together with preparations of carotene. In view of the fact that cases of carotenemia have arisen from overdosage the Council warns against the administration of too large doses of carotene. The vitamin potencies stated are on the basis of biological assays and not on physical and chemical measurements establishing the identity and purity of the product.

Dosage—See statement under vitamin A and D Preparations. Carotene is generally administered in the form of carotene dissolved in an oily solution.

WYETH INCORPORATED

Carotene in Oil 50 cc bottle. A solution containing carotene in cottonseed oil. It is biologically assayed to have in each gram a vitamin A potency of not less than 7500 units U S P. Accompanied by a dropper designed to deliver 25 drops to the cubic centimeter.

Carotene with Vitamin D Concentrate in Oil 50 cc bottle A solution in cottonseed oil of carotene with sufficient vitamin D concentrate to bring the assayed potency to not less than 1 000 U S P units per gram When assayed for vitamin A potency by the method of the U S P it is required to contain in each gram not less than 7 500 units

The vitamin D concentrate is used by license of Columbia University under U S patent 1 678 454 (July 24 19 28 exp'd)

OLEOVITAMIN A—Natural Vitamin A in Oil—Fish liver oil or fish liver oil diluted with an edible vegetable oil or a solution of vitamin A concentrate in fish liver oil or in an edible vegetable oil The vitamin A shall be obtained from natural (animal) sources Oleovitamin A contains in each Gm not less than 50 000 and not more than 60 000 U S P units of vitamin A and not more than 1 000 U S P units of vitamin D U S P

For description and standards see the U S Pharmacopeia under Oleovitamin A and Oleovitamin A Capsules

Actions Uses and Dosage See vitamin A and D preparations

ABBOTT LABORATORIES

Vitamin A Capsules Each capsule contains 25 000 U S P units of vitamin A derived from natural fish liver oils

INTERNATIONAL VITAMIN CORPORATION

Oleo Vitamin A Capsules Each capsule contains 25 000 U S P units of vitamin A derived from fish liver oils

McKesson & Robbins Inc

Concentrated Oleo Vitamins A and D 6 cc vials A concentrate of vitamins A and D prepared from cod liver oil the concentrate containing not less than 60 000 U S P units of vitamin A and not less than 10 000 U S P units of vitamin D per gram

WALKER VITAMIN PRODUCTS INC

Oleo Vitamin A Capsules Each capsule contains 25 000 U S P units of vitamin A derived from fish liver oils

WHITE LABORATORIES INC

White's Oleo Blend Vitamin A Capsules Each capsule contains 25 000 U S P units of vitamin A derived from fish liver oils

Vitamin B Complex Preparations

For allowable claims see preceding article Vitamin B Complex

The Council will consider for acceptance the following types of preparations containing mixtures of the components of the vitamin B complex

(1) Mixtures of pure thiamine riboflavin and nicotinic acid providing in the recommended daily intake 1 milligram thiamine 1.5 to 2 milligrams riboflavin 10 milligrams nicotinic acid or simple multiples thereof

(2) Dried yeast U S P having the following minimum vitamin content per gram 0.12 milligram thiamine 0.04 milligram riboflavin and 0.250 milligram nicotinic acid

(3) Dried yeast U S P as described under (2), to which has been added riboflavin and nicotinic acid in such quantities that for each milligram of thiamine contained in the finished product there are present 1.5 to 2 milligrams of riboflavin and 10 milligrams of nicotinic acid

(4) A concentrate of the vitamin B complex from brewer's yeast as described under (2) and providing in the recommended daily intake 1 milligram of thiamine (or a simple multiple thereof) and corresponding proportions of other known vitamins of yeast

(5) A concentrate of the vitamin B complex from liver containing in each gram not less than 0.25 milligram of riboflavin

(6) A concentrate of the vitamin B complex from brewer's yeast fortified with riboflavin and nicotinic acid and providing in the recommended daily intake 1 milligram thiamine 1.5 to 2 milligrams riboflavin and 10 milligrams nicotinic acid or simple multiples thereof

(7) A concentrate of the vitamin B complex from rice polish providing in the recommended daily intake 1 milligram thiamine 1.5 to 2 milligrams riboflavin and 10 milligrams of nicotinic acid or simple multiples thereof

DRIED YEAST—Dry Yeast—U S P—Dried Yeast consists of the dry cells of any suitable strain of *Saccharomyces cerevisiae* Meyen (Fam. *Saccharomycetaceae*) Dried Yeast may be obtained as a by product from the brewing of beer which has been made from an extract from cereal grain and hops The yeast cells are washed free of beer and dried and may or may not be debittered These yeasts are commonly known respectively as Brewer's Dried Yeast and (Debittered) Brewer's Dried Yeast Dried Yeast may also be obtained by growing suitable strains of yeast using media other than those required for the production of beer and under appropriate environmental conditions The yeast thus obtained is commonly known as Primary Dried Yeast If Dried Yeast is labeled to

show its source, it shall be labeled as 'Brewer's Dried Yeast,' 'Debittered Brewer's Dried Yeast,' or 'Primary Dried Yeast' whichever may be appropriate

"Dried Yeast contains not less than 40 per cent of protein and, in each Gm, the equivalent of not less than 0.12 mg of thiamine hydrochloride 0.04 mg of riboflavin and 0.25 mg of nicotinic acid"—U S P.

For further description and standards see the First Bound Supplement to the U S Pharmacopeia XII under Dried Yeast and Dried Yeast Tablets

Actions and Uses—Yeast extract containing vitamin B complex is proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex in the diet

Dosage—Infants 2 cc to 4 cc of the liquid preparation daily, children 4 cc to 12 cc of the liquid preparation, adults 12 cc to 24 cc of the liquid preparation

ABBOTT LABORATORIES

Brewers' Yeast Powder Fortified with Riboflavin and Nicotinic Acid Contains dried brewers' yeast (*Saccharomyces cerevisiae*), debitterized, fortified with crystalline riboflavin and nicotinic acid to contain in each gram vitamin B₁ 50 U S P units (0.15 mg) riboflavin 0.3 mg and nicotinic acid 1.5 mg Daily prophylactic dose for infants $\frac{1}{2}$ level teaspoon, children 1 to 6 years old 1 level teaspoon, children 6 to 12 years old $1\frac{1}{2}$ level teaspoons older children and adults 2 level teaspoons mixed with water, milk or fruit juices

Brewers' Yeast Tablets, 0.4 Gm, Fortified with Riboflavin and Nicotinic Acid Each tablet contains Abbott's Brewers Yeast Powder Fortified with Riboflavin and Nicotinic Acid 0.4 Gm providing in each tablet vitamin B₁ 20 U S P units (0.06 mg), riboflavin 0.12 mg, nicotinic acid 0.6 mg Average daily dose, as a supplement to the diet for children 6 to 12 years old 6 tablets, older children and adults, 9 tablets, therapeutic doses must be determined for each patient

Brewer's Yeast Tablets, 0.5 Gm, Fortified with Riboflavin and Nicotinic Acid Each tablet contains 0.5 Gm of dried brewers yeast (*Saccharomyces cerevisiae*) debitterized, fortified with crystalline riboflavin and nicotinic acid to contain in each tablet vitamin B₁ 35 U S P units (0.1 mg) riboflavin 0.2 mg and nicotinic acid 1 mg Prophylactic dose for adults 10 tablets daily therapeutic doses must be determined for each patient

Preparation—

Abbott's brewers yeast tablets are prepared from a selected strain of *Saccharomyces cerevisiae* especially cultured The yeast cells are washed and dried the dry powder containing approximately 5 per cent of moisture and compressed into tablets

The vitamin B₁ content of the tablets is determined by comparison with the international standard by the modified Smith rat curative method. The vitamin G content is determined by the Sherman Bourquin method.

H W KINNEY AND SONS

Kinney's Yeast Extract Containing Vitamin B Com-

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Preparation—

Kinney's yeast extract containing vitamin B complex is prepared by extracting specially cultured dried brewers yeast in an aqueous medium under proper conditions of pH control. The extract is concentrated and clarified. It is then preserved in liquid form by the addition of an equal volume of a mixture of equal parts of glycerin and simple syrup.

The thiamine
with the U S P
ing to the meth
Hydrochloride pa
riboflavin content
Riboflavin Assay,

The glycerin content is estimated according to the method described in "Methods of Analysis" A. O. A. C. 5th Edition 1940 page 396 chapter XXVIII paragraph 55.

MCNEIL LABORATORIES, INC

Brewers' Yeast Tablets 0.32 Gm. Each tablet contains brewers yeast 0.32 Gm. providing thiamine hydrochloride 0.167 mg. (55.5 U. S. P. units) riboflavin 0.023 mg. and niacin 0.195 mg.

Preparation—

Dried Brewers Yeast—U. S. P.—Granulated with a mixture of calcium carbonate, starch, sodium chloride, dried malt syrup, saccharin, vanillin, oil of chocolate and talc. The mixture is compressed into tablets.

MEAD JOHNSON AND COMPANY

Brewers' Yeast Powder 28.35 Gm. (11 level teaspoons or 3 level tablespoons). Each gram contains not less than thiamine (vitamin B₁) 0.18 mg., riboflavin (vitamin G) 0.06 mg. and niacin 0.4 r.

complex comm
infants ½ to 1
1 to 6 1 to 2

use as a supplement in the treatment of deficiencies of various factors of the vitamin B complex, dosage will depend on the type of specific vitamin therapy employed, the severity of the condition and the individual patient, in general, 2 to 4 level teaspoons daily. For supplementary use with specific vitamin therapy in ariboflavinosis and pellagra 7 or more level teaspoons daily.

Brewers' Yeast Tablets 0.4 Gm Each tablet contains 0.4 Gm dehydrated brewers' yeast supplying thiamine hydrochloride 0.06 mg, riboflavin 0.02 mg and 0.15 mg niacin together with other factors of the vitamin B complex commonly occurring in brewers' yeast. Dosage for children 6 to 10 tablets daily, for adults 10 to 12 daily for pregnancy and lactation 12 to 20 tablets daily. For use as a supplement in the treatment of deficiencies of various factors of the vitamin B complex dosage will depend on the type of specific vitamin therapy employed, the severity of the condition and the individual patient, in general, 8 to 20 tablets daily. For supplementary use with specific vitamin therapy in ariboflavinosis and pellagra 35 or more tablets daily.

Preparation—

Mead's brewers' yeast powder is a dried nonviable strain of *Saccharomyces cerevisiae* cultured especially for its vitamin content. It is readily suspended in water, milk, tomato juice or other suitable fluids.

L. R. SQUIBB & SONS

Brewers' Yeast Tablets 0.4 Gm Each tablet contains 0.4 Gm dehydrated brewers' yeast supplying thiamine hydrochloride 0.06 mg, riboflavin 0.03 mg and niacin 0.15 mg.

VITAMIN B COMPLEX SYRUP—A syrup prepared from a concentrated extract of dried brewers' yeast and an extract of corn processed with *Clostridium acetobutylicum* with inverted cane sugar 40 per cent w/v and natural flavoring.

*Actions and Uses—*Proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex.

Vit Co Products Co

Vitamin B Complex Syrup Each 5 cc contains thiamine hydrochloride 1.5 mg, riboflavin 1.0 mg, pyridoxine hydrochloride 0.5 mg and nicotinic acid 7.0 mg with other vitamin B complex factors as extracted from 10 Gm of dried brewers' yeast.

U. S. Patent 2,193,876 (March 19, 1940; expires 1955)

Thiamine Preparations

For allowable claims see preceding article Thiamine

THIAMINE HYDROCHLORIDE U. S. P.—Thiamine hydrochloride—Vitamin B₁ hydrochloride—Vitamin B— $C_{12}H_{17}ClN_4OS$
OS·HCl U. S. P.—Betabion

For description and standards see the U. S. Pharmacopeia under Thiamine Hydrochloride and Thiamine Hydrochloride Tablets. One mg of thiamine hydrochloride is equivalent to 333 U. S. P. units.

Acceptance of tablets thiamine hydrochloride will be limited to $\frac{1}{2}$, 1, 3, 5 and 10 mg of thiamine hydrochloride per tablet, and the acceptance of solutions thiamine hydrochloride for parenteral use will be limited to 1, 5, 10 and 50 mg thiamine hydrochloride per cc

Actions and Uses—See preceding article Thiamine

Dosage—The minimum daily requirement of thiamine for an adult appears to be approximately 1 mg, and the optimum intake is said to lie between 15 and 25 mg. For the child the optimum intake may be calculated from the caloric requirement by allowing at least 0.03 milligram for each 100 calories. In the well balanced diet the thiamine requirement should be obtained from the food.

When pharmaceutical preparations of thiamine hydrochloride are prescribed the minimum daily prophylactic dosage for the infant should not be less than 0.15 mg and for the adult should not be less than 1 mg. There appears to be no satisfactory evidence that prophylactic dosages in excess of 0.5 mg for the infant and 3 mg for the adult are indicated. Evidence on which to base dosages in the treatment of acute deficiencies is meager. There are indications that doses of the order of 10 to 50 mg may be advantageous in specific instances. There is no evidence that doses considerably in excess of these quantities have a toxic effect.

ABBOTT LABORATORIES

Tablets Thiamine Hydrochloride 1 mg, 3 mg, 5 mg and 10 mg

Sterile Isotonic Solution Thiamine Hydrochloride, 10 mg per cc, 10 cc bottle. Each cc contains thiamine hydrochloride 10 mg, sodium chloride 57 mg and chlorobutanol 5 mg in chemically pure water. This preparation is for parenteral administration.

Sterile Solution Thiamine Hydrochloride, 50 mg per cc, 5 cc bottle. Each cc contains thiamine hydrochloride 50 mg and chlorobutanol 5 mg in chemically pure water. This preparation is for parenteral administration.

AMERICAN PHARMACEUTICAL CO., INC.

Tablets Thiamine Hydrochloride 1 mg, 5 mg and 10 mg

GEORGE A. BREXON & COMPANY, INC.

Tablets Thiamine Hydrochloride 1 mg, 5 mg and 10 mg

Solution Thiamine Hydrochloride, 10 mg per cc, 10 cc. vial. Contains sodium chloride 75 mg per cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Solution Thiamine Hydrochloride, 50 mg per cc, 5 cc. Contains sodium chloride 365 mg per cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

BURROUGHS WELLCOME & Co, Inc

Hypoloid Solution Thiamine Hydrochloride, 10 mg per cc 1 cc ampuls

Hypoloid Solution Thiamine Hydrochloride, 50 mg per cc 5 cc vials Preserved with phenol 0.5 per cent

Tabloid Thiamine Hydrochloride 1 mg 5 mg and 10 mg

BRISTOL LABORATORIES, INC

Solution Thiamine Hydrochloride, 10 mg per cc 1 cc ampuls and 5 cc and 10 cc vials Each cubic centimeter contains 3.333 international units of crystalline vitamin B₁ hydrochloride 5 mg of chlorobutanol in double distilled water

Solution Thiamine Hydrochloride 50 mg per cc 1 cc ampuls and 5 cc and 10 cc vials Each cubic centimeter contains 16.666 international units of crystalline vitamin B₁ hydrochloride 5 mg of chlorobutanol in double distilled water

THE DRUG PRODUCTS CO., INC

Pulvoids Thiamine Hydrochloride 1 mg 3 mg

Solution of Thiamine Hydrochloride, 10 mg per cc 1 cc ampul hyposols

Solution of Thiamine Hydrochloride, 50 mg per cc 1 cc ampul hyposols

Solution of Thiamine Hydrochloride, 10 mg per cc 10 cc hypsol vials Preserved with 0.5 per cent of chlorobutanol

Solution of Thiamine Hydrochloride, 50 mg per cc 10 cc hypsol vials Preserved with 5 mg of chlorobutanol

ENDO PRODUCTS, INC

Tablets Thiamine Hydrochloride 1 mg 3 mg and 5 mg

Solution Thiamine Hydrochloride, 1 mg per cc 1 cc ampuls Preserved with 0.5 per cent chlorobutanol

Solution Thiamine Hydrochloride 10 mg per cc 1 cc ampuls and 10 cc vials Preserved with 0.5 per cent chlorobutanol

Solution Thiamine Hydrochloride 50 mg per cc 5 cc and 10 cc vials Preserved with 0.5 per cent chlorobutanol

FLINT, EATON & COMPANY

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

Solution Thiamine Hydrochloride, 10 mg per cc
1 cc ampuls

HORTON & CONVERSE

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

INTERNATIONAL VITAMIN CORPORATION

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

McKesson & Robbins, Inc

Tablets Thiamine Hydrochloride 0.5 mg 1 mg and 3 mg

MEAD JOHNSON AND COMPANY

Tablets Thiamine Hydrochloride 1 mg

MERCK & Co. Inc

Betabion (Powder) Thiamine hydrochloride 1 Gm bottle
U. S. trademark 336 518

Thiamine Hydrochloride (Powder)

THE WM. S. MERRELL COMPANY

Tablets Thiamine Hydrochloride 1 mg 3 mg 5 mg
and 10 mg

NATIONAL DRUG COMPANY

Tablets Thiamine Hydrochloride 1 mg

Solution Thiamine Hydrochloride, 10 mg per cc 1 cc
and 10 cc ampuls

Solution Thiamine Hydrochloride, 50 mg per cc 5 cc
ampul vials

SCHIEFFELIN & Co

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

CARROLL DUNHAM SMITH PHARMACEUTICAL COMPANY

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

Solution Thiamine Hydrochloride, 10 mg per cc 1 cc
ampuls Each cubic centimeter contains thiamine hydrochloride
10 mg in isotonic solution of sodium chloride preserved with
0.5 per cent chlorobutanol

SMITH DORSEY COMPANY

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

Solution Thiamine Hydrochloride 10 cc vials 10 mg per cc and 50 mg per cc Each cubic centimeter contains thiamine hydrochloride in an isotonic solution of sodium chloride Chlorobutanol 0.5 per cent added as a preservative

E. R. SQUIBB & SONS

Crystals Thiamine Hydrochloride 1 Gm bottle

Tablets Thiamine Hydrochloride 1 mg 3 mg, 5 mg and 10 mg

Solution Thiamine Hydrochloride, 50 mg per cc 10 cc vials Preserved with 0.5 per cent of chlorobutanol

FREDERICK STEARNS & COMPANY DIVISION

Tablets Thiamine Hydrochloride 1 mg 5 mg and 10 mg

Solution Thiamine Hydrochloride 50 mg per cc 5 cc vial Made isotonic with sodium chloride and preserved with 0.5 per cent of chlorobutanol

THE UPJOHN COMPANY

Tablets Thiamine Hydrochloride 1 mg 3 mg 5 mg and 10 mg

Solution Thiamine Hydrochloride 5 mg per cc 1 cc ampuls Preserved with 0.5 per cent of chlorobutanol

Solution Thiamine Hydrochloride, 10 mg per cc 1 cc ampuls and 10 cc vials Preserved with 0.5 per cent of chlorobutanol

Solution Thiamine Hydrochloride, 50 mg per cc 5 cc and 10 cc vials Preserved with 0.5 per cent of chlorobutanol

WALKER VITAMIN PRODUCTS INC

Solution Thiamine Hydrochloride 15 cc and 60 cc bottles 100 International units vitamin B₁ per drop

Tablets Thiamine Hydrochloride 1 mg 3 mg 5 mg and 10 mg

WARREN TEEB PRODUCTS COMPANY

Tablets Thiamine Hydrochloride 10 mg

WHITE LABORATORIES, INC

Tablets Thiamine Hydrochloride 5 mg

WYETH, INCORPORATED

Tablets Thiamine Hydrochloride 5 mg and 10 mg

Solution Thiamine Hydrochloride, 50 mg per cc • 5 cc ampuls Preserved with 0.5 per cent of chlorobutanol

Mixed Vitamin B Components

TRIASYN B—Triasyn B Capsules and Tablets contain in each capsule or tablet not less than 1 mg of thiamine hydrochloride 1.5 mg of riboflavin and 10 mg of nicotinamide—U S P

For description and standards see U S Pharmacopoeia XII First Bound Supplement under Triasyn B Capsules and Triasyn B Tablets

Actions Uses and Dosage—For prophylaxis and treatment of conditions arising from deficiency of thiamine riboflavin and nicotinic acid See articles on the various vitamins concerned

PREMO PHARMACEUTICAL LABORATORIES, INC

Tablets Triasyn B Each tablet contains 1 mg of thiamine hydrochloride 1.5 mg of riboflavin and 10 mg of nicotinic acid amide

Capsules Triasyn B Each capsule contains 1 mg of thiamine hydrochloride, 1.5 mg of riboflavin and 10 mg of nicotinic acid amide

Riboflavin Preparations

For allowable claims see preceding article, Riboflavin.

RIBOFLAVIN—Lactoflavin—Vitamin B₂—Vitamin G— $C_{17}H_{19}N_4O_6$ U S P

For description and standards see the U S Pharmacopoeia under Riboflavin and Riboflavin Tablets

Acceptance of tablets riboflavin will be limited to 1 2 5 and 10 mg of riboflavin per tablet and the acceptance of solutions riboflavin for parenteral use will be limited to 0.2 mg Riboflavin per cc except that special consideration will be given to solutions of higher concentrations that may be obtained by the use of other reagents

Actions and Uses—See preceding article Riboflavin

Dosage—The optimum intake of riboflavin for an infant appears to be approximately 1 mg per day and for an adult approximately 3 mg per day The requirement during pregnancy and lactation is higher When riboflavin is used ther-

apeutically the dosage varies from 2 to 10 mg per day depending upon the severity of the deficiency. No side effects have been noticed following the administration of relatively large doses.

ABBOTT LABORATORIES

Capsules Riboflavin 1 mg and 5 mg

Tablets Riboflavin 1 mg and 5 mg

AMERICAN PHARMACEUTICAL CO INC

Tablets Riboflavin 1 mg and 5 mg

GEORGE A BRON & COMPANY INC

Tablets Riboflavin 1 mg and 5 mg

BURROUGHS WELLCOME & CO INC

Tablet Riboflavin 1 mg

INDO PRODUCTS INC

Tablets Riboflavin 5 mg

HOFFMANN LAROCHE INC

Solution Riboflavin 0.5 mg per cc. 2 cc ampuls. Contains urea 10 per cent (w/v) to maintain riboflavin in solution.

INTERNATIONAL VITAMIN CORPORATION

Tablets Riboflavin 1 mg and 5 mg

LAKESIDE LABORATORIES

Tablets Riboflavin 1 mg and 5 mg

MEAD JOHNSON AND COMPANY

Tablets Riboflavin 1 mg and 5 mg

MERCK & CO INC

Riboflavin (Powder)

THE WM S MENDEL COMPANY

Tablets Riboflavin 1 mg

PREMO PHARMACEUTICAL LABORATORIES INC

Tablets Riboflavin 1 mg 2 mg and 5 mg

THE UPJOHN COMPANY

Tablets Riboflavin 1 mg

WALKER VITAMIN PRODUCTS INC

Tablets Riboflavin 1 mg and 5 mg

WILLIAM R. WARNER & Co., INC.

Tablets Riboflavin 1 mg

WARREN TEED PRODUCTS COMPANY

Tablets Riboflavin 1 mg

Nicotinic Acid and Nicotinamide Preparations

For allowable claims see preceding article Nicotinic Acid and Nicotinamide

NICOTINIC ACID — *Niacin* — When dried for three hours over sulfuric acid contains not less than 99.5 per cent of $\text{HC}_6\text{H}_4\text{O}_2\text{N}$ U S P

For description and standards see the U S Pharmacopeia under Nicotinic Acid and Nicotinic Acid Tablets



Acceptance of nicotinic acid tablets will be limited to 25, 50 and 100 mg. of nicotinic acid per tablet. Solutions of nicotinic acid will not be eligible for acceptance.

Actions and Uses — See preceding article Nicotinic Acid and Nicotinamide

Dosage — The optimum intake of nicotinic acid has not been established with certainty. However for adults it seems to be of the order of 15 to 20 mg. per day. The dose for therapeutic purposes varies considerably from person to person depending upon the severity of the deficiency and possibly upon other as yet unknown factors. The maximum quantity to be recommended is 500 mg. per day given in 10 doses of 50 mg. each.

ANNOTT LABORATORIES

Tablets Nicotinic Acid 50 mg. and 100 mg.

AMERICAN PHARMACEUTICAL CO., INC.

Nicotinic Acid (*Powder*) 30 Gm., 120 Gm. and 450 Gm. packages

Tablets Nicotinic Acid 25 mg., 50 mg. and 100 mg.

GEORGE A. BERON & COMPANY, INC.

Tablets Nicotinic Acid 100 mg.

BURROUGHS WELLCOME & Co INC

Tabloid Nicotinic Acid 50 mg and 100 mg

ENDO PRODUCTS, INC

Tablets Nicotinic Acid 50 mg and 100 mg

LINT EATON & COMPANY

Tablets Nicotinic Acid 25 mg

INTERNATIONAL VITAMIN CORPORATION

Tablets Nicotinic Acid 25 mg 50 mg and 100 mg

LAKE SIDE LABORATORIES INC

Tablets Nicotinic Acid 50 mg

MEAD JOHNSON AND COMPANY

Tablets Niacin 25 mg

MERCK & Co INC

Niacin (*Powder*)

THE WM S MERRELL COMPANY

Tablets Nicotinic Acid 50 mg

NATIONAL DRUG COMPANY

Tablets Nicotinic Acid 50 mg and 100 mg

THE NEW YORK QUININE AND CHEMICAL WORKS INC

Nicotinic Acid (*Powder*) bulk

PARKE DAVIS & COMPANY

Tablets Nicotinic Acid 50 mg and 100 mg

PITMAN MOORE COMPANY

Tablets Nicotinic Acid 50 mg

SMITH DORSEY COMPANY

Tablets Nicotinic Acid 50 mg and 100 mg

THE UPJOHN COMPANY

Tablets Nicotinic Acid 50 mg and 100 mg

WALKER VITAMIN PRODUCTS INC

Tablets Niacin 25 mg 50 mg and 100 mg

WILLIAM R. WARNER & Co., INC

Tablets Nicotinic Acid 50 mg

WARREN TEED PRODUCTS COMPANY

Tablets Niacin 50 mg

NICOTINAMIDE—Nicotinic Acid Amide—Niacinamide
— When dried over sulfuric acid for 18 hours contains not less than 98.5 per cent of $C_6H_6N_2O$ U S P

For description and standards see the U S Pharmacopeia under Nicotinamide and Nicotinamide Tablets

Acceptance of nicotinamide tablets will be limited to 25, 50 and 100 mg nicotinamide per tablet and the acceptance of ampul solutions for parenteral use will be limited to 25, 50 and 100 mg of nicotinamide per cubic centimeter

Actions and Uses—See preceding article Nicotinic Acid and Nicotinamide

Dosage—Same as for nicotinic acid

ABBOTT LABORATORIES

Nicotinamide (*Powder*) bulk

Sterile Solution Nicotinamide, 100 mg per 2 cc 2 cc ampuls

Tablets Nicotinamide 50 mg and 100 mg

AMERICAN PHARMACEUTICAL CO., INC

Tablets Nicotinamide 50 mg

GEORGE A. BRUN & COMPANY, INC

Solution Nicotinic Acid Amide, 25 mg per cc 2 cc ampuls

Tablets Nicotinamide 100 mg

Tablets Nicotinic Acid Amide 50 mg

BURROUGHS WELLCOME & Co., INC

Hypoloid Nicotinamide Injection, 100 mg per cc 5 cc vial Preserved with 0.5 per cent chlorobutanol

THE DRUG PRODUCTS CO., INC

Hyposol Solution of Nicotinamide 50 mg per cc 1 cc ampuls and 10 cc vials Preserved with 0.5 per cent of chlorobutanol

Pulvoids Nicotinamide 50 mg

Vitamin B₁₂

(2004)

It may be isolated from natural sources or prepared synthetically from ethoxy acetylacetone and cyanoacetamide.

Actions and Uses—The nutritive and therapeutic value of pyridoxine hydrochloride has not been definitely established. It has been accepted by the Council for purposes of standardization and experimentation only.

Dosage—A dose of 5 to 10 mg daily is suggested

Tests and Standards—

Pyridoxine hydrochloride occurs as a white odorless, crystalline powder which melts with decomposition between 200 and 212 C. Under the polarising microscope it appears as thick, birefringent rods and broken fragments. When recrystallized from methanol containing a few drops of concentrated hydrochloric acid needle-shaped crystals are obtained which are birefringent and exhibit oblique extinction. In the crystalline state it is reasonably stable to light and air. Acidic aqueous solutions of pyridoxine hydrochloride are stable and may be heated for thirty minutes at 120 C without decomposition. It is soluble in water (22 Gm per hundred cubic centimeters), slightly soluble in 95 per cent ethanol (11 Gm. per hundred cubic centimeters), sparingly soluble in acetone, practically insoluble in ether. Aqueous solutions are acidic (pH about 3.0 for a concentration of 10 mg per cubic centimeter) produce a red color with ferric chloride solution, yield a precipitate with phosphotungstic acid solution and yield a precipitate with silver nitrate solution which is insoluble in nitric acid but soluble in ammonia water.

Dissolve a few crystals of pyridoxine hydrochloride in 2 cc. of alcohol. Add 2 drops of 10 per cent ammonium hydroxide solution and 1 cc. of 2,6-dichloroquinone chloranil solution (0.01 per cent in alcohol) a deep blue color forms on standing.

| | | | |
|----------|----|-----------------------------|-----------------------|
| Char 0.4 | Gm | of pyridoxine hydrochloride | Boil the ebarred mass |
| with a - | | | water, |
| filter, | | | dissolve |
| the res | | | to 5 |
| ec, wit | | | y color |
| produe | | | g 0.02 |
| mg of | | | |

When dried over sulfonic acid anhydrous calcium sulfate or anhydrous magnesium perchlorate for twenty four hours the loss in weight does not exceed 0.2 per cent.

Determine the carbon and hydrogen content by combustion. The carbon content is not less than 46.5 nor more than 46.9 per cent, the hydrogen content is not less than 5.6 nor more than 6.0 per cent. The residue from the carbon hydrogen determination, or from an ash determination, does not exceed 0.05 per cent.

Determine the nitrogen content the amount found is not less than 6.6 nor more than 6.9 per cent

Method of Assay for Tablets and Solutions

The following reagents are necessary

1. **Barbital Buffer**—Dissolve 18.0 Gm sodium diethylbarbiturate in 700 cc of distilled water and titrate with normal hydrochloric acid to a pH of 7.5 to 7.7 using a glass electrode. Filter off the precipitate.

of diethylbarbituric acid (If the buffer is allowed to stand over twenty four hours, the pH must be readjusted with either normal hydrochloric acid or normal sodium hydroxide to a pH of 7.5 to 7.7)

2 Chloroimide Reagent—Dissolve 250 mg. 2,6-dichloroquinone chloroimide in 100 cc of acid free butanol. If the reagent is to be kept for some time, it must be stored in a brown, glass stoppered bottle at refrigerator temperatures, treated thus, it is stable for about two weeks.

3 Standard Solution—100 mg of dried crystalline pyridoxine hydrochloride is dissolved in exactly 100 cc of absolute alcohol. If the solution is to be used immediately, 95 per cent ethanol may be employed. (In the absence of a microbalance, a larger quantity may be weighed and appropriate dilutions made from the more concentrated stock solution.)

Procedure—Dilute the pyridoxine solution to a final concentration in per cubic centimeter. In the case of more—are transferred to a volumetric flask shaken to disintegrate the tablet. The solution is filtered, the first 25 cc discarded and the next 25 cc saved for the test.

In the following procedures the preparation of the standard and unknown must be carried on concurrently to allow the same amount of time for the development of color in the two solutions.

Transfer 50 cc of the solution to be tested (after diluting as indicated) to a 50 cc volumetric flask. Add 50 cc of the barbital buffer and 20 cc of ethanol.

Prepare a standard comparison solution by transferring 50 cc of the standard pyridoxine hydrochloride solution to a 50 cc volumetric flask, adding 50 cc of barbital buffer, 15 cc of ethanol and 5 cc of water.

Now add to both solutions 50 cc of butanol chloroimide reagent, start timing and shake intermittently for twenty minutes. Dilute to the mark with ethanol and compare in a colorimeter. The pyridoxine hydrochloride found is not less than 93 or more than 107 per cent.

ENDO PRODUCTS, INC.

Solution Pyridoxine Hydrochloride: 1 cc ampuls of 25 mg and 50 mg per cc and 10 cc vials of 50 mg per cc

LAKESIDE LABORATORIES, INC.

Pyridoxine Hydrochloride, 50 mg. per cc.: 1 cc. ampuls and 5 cc. vials

Tablets Pyridoxine Hydrochloride: 20 mg

MERCK & CO, INC.

Hexabione Hydrochloride (Crystals): 100 mg bottles

U S trademark 377,657

Vitamin B₆ Hydrochloride (Powder).

SMITH-DORSEY COMPANY

Tablets Pyridoxine Hydrochloride: 1 mg

THE UPJOHN COMPANY

Sterile Solution Pyridoxine Hydrochloride 50 mg in 2 cc ampuls

Tablets Pyridoxine Hydrochloride 10 mg

WILLIAM R. WARNER & Co., INC.

Tablets Pyridoxine Hydrochloride 5 mg

Pyridoxine Hydrochloride 1 cc ampuls Each cubic centimeter contains pyridoxine hydrochloride 25 mg and sodium phosphate U S P 75 mg

WYETH INCORPORATED

Solution Pyridoxine Hydrochloride 50 mg in 1 cc ampuls

Ascorbic Acid Preparations

For allowable claims see preceding article Ascorbic Acid

ASCORBIC ACID—Vitamin C—U S P—Cebione—Cevitamic acid—Contains when dried in a vacuum desiccator over sulfuric acid for 3 hours not less than 99 per cent of $C_6H_8O_6$ U S P

For description and standards see the U S Pharmacopeia under Ascorbic Acid and Ascorbic Acid Tablet

Ascorbic acid is quite stable but in impure preparations and in many natural products the vitamin oxidizes on exposure to air or light and such products should be preserved in an oxygen free atmosphere protected from light

Acceptance of tablets of ascorbic acid will be limited to 10, 25, 50 and 100 mg of ascorbic acid per tablet

Actions and Uses—See preceding article Ascorbic Acid

Dosage—The optimum daily intake of ascorbic acid for an infant appears to be approximately 30 mg., and for an adult approximately 75 mg. Under certain conditions notably pregnancy and lactation the requirement of the adult may be as high as 100 or 150 mg.

When pharmaceutical preparations are prescribed the protective dose for infants is 10 mg daily and the therapeutic dose is 30 to 50 mg daily. The protective dose for adults is 25 mg daily and the therapeutic dose is 100 to 150 mg daily. Each 1 mg is equivalent to 20 international units of vitamin C. No evidence exists that ten fold increases exert detrimental effects.

ABOTT LABORATORIES

Tablets Ascorbic Acid 25 mg, 50 mg and 100 mg

AMERICAN PHARMACEUTICAL CO INC

Ascorbic Acid (*Crystals*) 1 ounce and 5 ounce packages

Tablets Ascorbic Acid 25 mg 50 mg and 100 mg

GEORGE A BREON & COMPANY, INC

Tablets Ascorbic Acid 25 mg 50 mg and 100 mg

BURROUGHS WELLCOME & CO INC

Tabloid Ascorbic Acid 25 mg and 100 mg

INTERNATIONAL VITAMIN CORPORATION

Tablets Ascorbic Acid 25 mg 50 mg and 100 mg

MEAD JOHNSON AND COMPANY

Tablets Ascorbic Acid 25 mg and 100 mg

MERCK & CO INC

Cebione (*Crystals*) 10 Gm bottles

Tablets Cebione 10 mg 25 mg and 50 mg

U S Trademark 318 171

THE WM S MERRELL COMPANY

Tablets Ascorbic Acid 25 mg, 50 mg and 100 mg

NATIONAL DRUG COMPANY

Tablets Ascorbic Acid 25 mg

PARKE DAVIS & COMPANY

Tablets Ascorbic Acid 25 mg and 100 mg

Solution of Ascorbic Acid 2 cc glaseptic ampuls Each cubic centimeter contains 50 mg of ascorbic acid and 0.1 per cent of sodium bisulfite added as a preservative

PITMAN MOORE COMPANY

Tablets Ascorbic Acid 50 mg

SCHIEFFELIN & CO

Tablets Ascorbic Acid 25 mg and 50 mg

CARROLL DUNHAM SMITH PHARMACAL COMPANY

Tablets Ascorbic Acid 100 mg

SMITH DORSEY COMPANY

Tablets Ascorbic Acid 25 mg 50 mg and 100 mg

E. R. SQUIBB & SONS

Tablets Ascorbic Acid: 25 mg, 50 mg and 100 mg

FREDERICK STARNES & COMPANY DIVISION

Tablets Ascorbic Acid: 25 mg, 50 mg and 100 mg

THE UPJOHN COMPANY

Tablets Ascorbic Acid: 25 mg, 50 mg and 100 mg

WALKER VITAMIN PRODUCTS, INC.

Tablets Ascorbic Acid: 25 mg, 50 mg and 100 mg

WYETH, INCORPORATED

Tablets Ascorbic Acid: 25 mg and 100 mg

SODIUM ASCORBATE—The sodium salt of cevitamic acid, $C_6H_7O_6Na$

Actions and Uses—Sodium ascorbate possesses the activity of ascorbic acid and is preferred when parenteral therapy is indicated

Dosage—Same as for ascorbic acid

Tests and Standards—

A solution of sodium ascorbate may be prepared by neutralizing a solution of ascorbic acid with sodium hydroxide. The *pH* of sodium ascorbate solution is between 5.5 and 5.9. The ascorbic acid used in the preparation of Council accepted solutions of sodium ascorbate conforms to the tests and standards for ascorbic acid U. S. P.

GEORGE A. BREON & COMPANY, INC.

Solution Sodium Ascorbate: 2 cc ampuls. Each 2 cc contains sodium ascorbate equivalent to 100 mg (2,000 international units) ascorbic acid in sterile aqueous solution

Solution Sodium Ascorbate: 500 mg in 10 cc ampuls

Vitamin D Preparations or Preparations Giving Vitamin D Effect

For allowable claims see preceding article, Vitamin D

COD LIVER OIL WITH VIOSTEROL (See under Vitamins A and D Preparations)

HALIBUT LIVER OIL WITH VIOSTEROL (See under Vitamins A and D Preparations)

SYNTHETIC OLEOVITAMIN D—Viosterol in Oil (Applying only to Activated Ergosterol in Oil)—U S P—Irradiated Ergosterol in Oil—"A solution of activated ergosterol, or activated 7-dehydro-cholesterol, in an edible vegetable oil. Synthetic Oleovitamin D contains in each Gm not less than 10,000 U S P units of vitamin D

Synthetic Oleovitamin D must be labeled to indicate whether it contains activated ergosterol (*Vitamin D₂* or *Viosterol*) or whether it contains activated 7-dehydro cholesterol (*vitamin D₃*)." U S P Preparations listed under the title, Viosterol in Oil, contain activated ergosterol

For description and standards see the U S Pharmacopeia under *Synthetic Oleovitamin D*

Actions and Uses—See preceding article Vitamin D

Dosage—Daily prophylactic dose for the average infant, 5 drops (approximately 0.1 cc or $1\frac{1}{3}$ minims), for the premature and rapidly growing infant 15 drops (0.31 cc, 5 minims), daily curative dose, 15 to 20 drops (0.31 to 0.41 cc, 5 to 7 minims), in severe cases, doses in excess of 20 drops may be given. The marketed preparations are accompanied by a standard dropper designed to deliver 3 drops to the minim

Preparation—

Viosterol in Oil is prepared by either of the following methods

(a) Irradiation of a solution of purified ergosterol by ultra violet rays under a determined distance and intensity for a definite length of time, under reflux in an inert atmosphere. After irradiation the solution is concentrated and the majority of the unchanged ergosterol is removed. The remaining solvent is distilled in an inert atmosphere and the irradiated ergosterol is dissolved in a known weight of vegetable oil. The resulting oil solution is adjusted by admixture of a bland vegetable oil so that the final product when assayed by the U S P method has a vitamin D potency of not less than 10,000 U S P units per Gm

U S patents 1,680,818 (August 14, 1928, expired) and 1,871,136 (August 9, 1932, expires 1949) by license of the Wisconsin Alumni Research Foundation

(b) Activation of purified ergosterol by low velocity electrons after which the activated ergosterol is separated and dissolved in vegetable oil. The resulting solution is adjusted by admixture of a bland vegetable oil so that the final product when assayed by the U S P method has a vitamin D potency of not less than 10,000 U S P units per Gm

Manufactured by General Mills Inc. Special Commodities Division under license agreement with E. I. du Pont de Nemours & Company. U S patent 2,117,100 (May 10, 1938, expires 1955)

ABBOTT LABORATORIES

Viosterol in Oil 5 cc 20 cc and 50 cc bottles Viosterol in sesame oil

AMERICAN PHARMACEUTICAL CO INC

Viosterol in Oil 10 cc and 50 cc bottles Viosterol in vegetable oil

HOSPITAL LIQUIDS INC

Viosterol in Oil 50 cc bottle Viosterol in bland vegetable oil

INTERNATIONAL VITAMIN CORPORATION

Viosterol in Oil 10 cc and 60 cc bottles Viosterol in neutral vegetable oil

McKesson & Robbins Inc

Viosterol in Oil 10 cc and 60 cc bottles Viosterol in neutral vegetable oil

MEAD JOHNSON AND COMPANY

Viosterol in Oil 10 cc and 50 cc bottles Viosterol in corn oil

THE WM S MERRELL COMPANY

Viosterol in Oil 6 cc and 60 cc bottles Viosterol in vegetable oil

PARKE DAVIS & COMPANY

Viosterol in Oil 5 cc and 50 cc bottles Viosterol in corn oil

L R SQUIBB & SONS

Viosterol in Oil 5 cc 20 cc and 50 cc bottles Viosterol in corn oil

FREDERICK STEAPNS & COMPANY DIVISION

Viosterol in Oil 6 cc vials Viosterol in vegetable oil

WINTHROP CHEMICAL COMPANY, INC

Viosterol in Oil 5 cc and 50 cc bottles Viosterol in sesame oil

VITAMIN D₂—Drisdol—9||10 Ergostatriene (18 10 5 6 7 8 22 23)-ol 3 -C₂₈H₄₄O

Vitamin D₂ may be prepared by ultraviolet irradiation of ergosterol in a suitable solvent or by electronic bombardment of the compound. It is not identical with the vitamin D which predominates in fish liver oils and which is called vitamin D₃. A method of preparation of vitamin D₂ is given in Addendum 1936 to the British Pharmacopeia, 1932, page 20. The crystals have a potency of 40 units of vitamin D (U. S. P.) per microgram. (For methods of assay see U. S. P. XII, p. 640.)

Actions and Uses—1 or allowable claims, see under allowable claims for vitamin D

Tests and Standards—

Vitamin D₂ occurs as a colorless odorless acicular, crystalline substance. It is insoluble in water, soluble in alcohol, ether, chloroform, acetone, ethylene glycol and propylene glycol, sparingly soluble in vegetable oils. The melting point of vitamin D₂ lies between 115 and 118°C. Solutions of vitamin D₂ possess an absorption maximum at 2640 angstroms.

Dissolve approximately 0.5 mg of vitamin D₂ in 5 cc of chloroform add 3 drops of acetic anhydride and 3 drops of sulfuric acid and shake the mixture, a bright red color develops which rapidly changes to violet blue and finally to green.

Dissolve 0.03 Gm. of vitamin D₂ and 0.03 Gm. of 3,5 dinitrobenzoyl chloride in separate 1 cc portions of anhydrous pyridine. Mix the solution and warm the mixture on the water bath for ten minutes; add 5 cc of water, filter and wash the precipitate repeatedly with small amounts of cold water. Recrystallize the precipitated dinitrobenzoyl derivative twice from acetone and finally dry it in a desiccator under partial vacuum; the melting point of the product is from 147 to 149 C.

The specific rotation $[\alpha]_{\text{D}}^{25}$ of the vitamin D₂ dinitrobenzoate dissolved in acetone + 80 degrees

Dissolve approximately 0.01 Gm of vitamin D₂ in 1 cc of alcohol and add 1 cc of a 1 per cent solution of digitonin in 90 per cent alcohol allow the mixture to stand for twelve hours no precipitate occurs (absence of ergasterol)

of vitamin D₂ accurately weighed
are the solution in a 0.5 decimeter
the specific rotation lies between
remove the amount of carbon and
burning the substance in an appro-
content should not be less than
cent the hydrogen content should
more than 11.3 per cent

WINTHROP CHEMICAL COMPANY, INC.

Capsules Drisdol Concentrated Solution in Oil 5 minims Each capsule contains 125 mg of Drisdol and has a potency of 50 000 units of vitamin D (U S P)

Drisdol in Propylene Glycol 5 cc and 50 cc bottles. Each 1 cc contains 0.25 mg of drisdol and has a potency of 10,000 units of vitamin D (U S P) per gram. The propylene glycol used in the preparation of this product complies with the standards for propylene glycol N N R.

Dosage—Average daily dose 2 drops dissolved in total ration of modified or whole milk. If administered in water, gruel, etc. 4 drops daily for the average infant and up to 15 drops daily

for the premature or rapidly growing infant. Daily curative dose 15 to 20 drops. The product is marketed with a special dropper delivering 250 U S P units of vitamin D per drop.

U S patent 1 902 85 (March 21, 1933 exp res 1950) and 2 030 792 (Feb 11 1936 exp res 1953) and by license of the Wisconsin Alumni Research Foundation under U S patents 1 680 818 (Aug 14 1938 exp red) and 1 871 116 (Aug 9 1931 exp res 1949) U S trademark 1 11 661

Vitamins A and D Preparations

FISH LIVER OIL PREPARATIONS AND CONCENTRATES

The character of cod liver oil has been metabolized of calcium and phosphorus in general and particularly in the prevention of rickets. In fact the usual recommendation is

of cod liver oil also gives methods for the assay of its content of vitamin A and vitamin D. Furthermore it provides that the vitamin A potency and vitamin D potency of cod liver oil when designated shall be expressed in United States Pharmacopeia units per gram of oil and may be referred to as U S P units per gram of oil. It is also stipulated that

Cod liver oil must contain in each gram at least 850 U S P units of vitamin A and at least 85 U S P units of vitamin D. Cod liver oil may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in this pharmacopeia.

Obviously all brands in New and Nonofficial Remedies are required to have a vitamin potency of at least that of the pharmacopeial product.

Statements of the potency of tablet preparations of cod liver oil concentrate made on a "per tablet" basis and also on a "per gram of tablet" basis should appear in the firm's presentation and in New and Nonofficial Remedies. On the labels however a declaration of vitamin potency per tablet is sufficient.

At the present time a War Production Board order designed to conserve vitamin A supplies limits the quantity of vitamin A that can be recommended by a manufacturer to be taken daily to not more than 5000 units for many vitamin preparations. The order does not apply to U S P preparations or to preparations represented to contain 25000 or more U S P XI units of vitamin A in the smallest daily dosage recommended by the manufacturer or seller for adult use.

BLENDED OIL CONTAINING VITAMINS A AND D—A mixture of fish and/or vegetable oils to which viosterol may be added. The vitamin A content is not less than 1,800 U S P units per gram and the vitamin D content not less than 175 U S P units per gram.

Actions and Uses—See preceding article Vitamins A and D Preparations

Dosage—See preceding article Vitamins A and D Preparations

Blended oil containing vitamins A and D occurs as a thin liquid oil having a fishy but not rancid odor and a fishy taste. It is insoluble in water, slightly soluble in alcohol and soluble in chloroform, ether, benzene, ethyl acetate and carbon disulfide. The specific gravity is from 0.918 to 0.929 at 25°C. The refractive index is from 1.474 to 1.479 at 25°C.

A solution of one drop of blended oil containing vitamins A and D in 1 cc of chloroform when shaken with one drop of sulfuric acid acquires a blue color gradually changing to purple. Fill a tall cylindrical tube of about 120 cc capacity with the oil and maintain at 0°C for five hours; the oil remains clear and fluid and deposits no solid material.

Dissolve 2 Gm accurately weighed of Blended oil containing vitamins A and D in 100 cc of alcohol. Add 10 cc of a mixture with color which normal sodium matter in 15 per cent U S P 180 The 12

MEAD JOHNSON AND COMPANY

Mead's Blended Oil Containing Vitamins A and D
1 gallon bottles

U S patents 1,680,818 (Aug 14, 1923, expired) and 1,861,136 (Aug 9, 1934, expires 1951) under license of the Wisconsin Alumni Research Foundation

Irradiated ergosterol prepared by the method described under Mead's Viosterol in Oil is added to fish liver oil, sardine oil and maize oil, and the finished product is required to have a vitamin A potency of not less than 1,800 units (U S P) per gram and not less than 175 units (U S P) of vitamin D per gram.

CONCENTRATED OLEOVITAMIN A AND D—

Fish liver oil or fish liver oil diluted with an edible vegetable oil, or a solution of vitamin A and D concentrates in fish liver oil or in an edible vegetable oil. The vitamin A shall be obtained from natural (animal) sources and the vitamin D may be obtained from natural (animal) sources or may be synthetic oleovitamin D. Concentrated Oleovitamin A and D contains in each gram not less than 50,000 and not more than 65,000 U S P units of vitamin A and not less than 10,000 and not more than 13,000 U S P units of vitamin D. U S P

For description and standards see the U S Pharmacopeia under Concentrated Oleovitamin A and D

Actions, Uses and Dosage—See under Vitamin A and D preparations

WALKER VITAMIN PRODUCTS, INC

Concentrated Oleo Vitamin A-D Drops Each gram contains not less than 62 500 U S P units of vitamin A and Natural esters (stable oils) plus 1 with cinnamon

BURBOT LIVER OIL—The oil extracted from the livers of the Burbot (*Lota maculosa*), family Gadidae. It is biologically assayed to have a potency of not less than 4480 units of vitamin A (U S P) per gram and of not less than 640 units of vitamin D (U S P) per gram

Actions and Uses—Same as those of cod liver oil. See preceding article Vitamins A and D Preparations

Dosage—Prophylactic, 1 cc (40 drops) daily, or as prescribed by the physician. The product is marketed with a dropper designed to deliver about 25 drops to the cubic centimeter

Tests and Standards—

Burbot liver oil is a pale yellow oily liquid. It has a slightly fishy but not rancid odor and a fishy taste. It is slightly soluble in alcohol but is soluble in ether, chloroform, benzene, carbon disulfide and ethyl acetate. The specific gravity is from 0.921 to 0.927 at 25 C. The refractive index is from 1.479 to 1.482 at 20 C.

A solution of one drop of the oil in 1 cc of chloroform when shaken with one drop of sulfuric acid acquires a light violet color changing to violet dark green and finally brown. Treat 5 cc of oil with 5 cc of benzene and centrifuge for twenty-five minutes at 25 C. no precipitate forms and a clear solution remains.

Fill a tall cylindric standard oil sample bottle of about 120 cc capacity with burbot liver oil at a temperature between 23 and 28 C stopper and immerse the bottle in a mixture of ice and distilled water for five hours. the oil remains fluid and forms no deposit.

Dissolve 2 Gm of burbot liver oil accurately weighed in 20 cc of a mixture of equal volumes of alcohol and ether which previously has been neutralized with tenth normal sodium hydroxide using five drops of phenolphthalein T S as indicator and titrate with tenth normal sodium hydroxide to the production of a pink color which persists for fifteen seconds not more than 1 cc of tenth normal sodium hydroxide is required (free acid). The amount of unsaponifiable matter as determined by the method of U S P XI, page 446 is not less than 0.9 per cent nor more than 3.0 per cent. The saponification value as determined by the method of U S P XI page 445, is not less than 184 nor more than 196. The iodine value as determined by the method of U S P XI page 445 on 0.18 to 0.20 Gm of sample accurately weighed is not less than 155 nor more than 180.

BURBOT LIVER PRODUCTS Co

Burbot Liver Oil (Rowell) 60 cc and 240 cc bottles

Capsules Burbot Liver Oil (Rowell) 0.52 cc, minimums adjusted to have a potency of not less than 2215 units of vitamin A (U S P) and 315 units of vitamin D (U S P) per capsule

COD LIVER OIL—The partially destearinated fixed oil obtained from fresh livers of *Gadus morrhua* Linne and other species of the family *Gadidae*. *Cod Liver Oil* may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in the U S Pharmacopeia. Cod Liver Oil contains in each Gm at least 850 U S P units of Vitamin A and at least 85 U S P Units of Vitamin D

The Vitamin A potency and Vitamin D potency of Cod Liver Oil when designated shall be expressed in United States Pharmacopeia Units per gram of oil and may be referred to as 'U S P Units U S P

For description and standards see the U S Pharmacopeia under Cod Liver Oil

Actions Uses and Dosage—See preceding article Vitamins A and D Preparations

ABBOTT LABORATORIES

Cod Liver Oil 360 cc 480 cc and 384 liter bottles Each 1 Gm has a potency of not less than 1000 U S P units of vitamin A and of not less than 100 U S P units of vitamin D

BAY STATE LABORATORIES, INC

Cod Liver Oil 120 cc bottles Each gram contains 2500 U S P units of vitamin A and 125 U S P units of vitamin D

BONCHERDT MALT EXTRACT COMPANY

Malt Extract with Cod Liver Oil 480 cc bottles Each 100 cc contains cod liver oil 25 cc and malt extract 75 cc. Each 1 Gm has a potency of not less than 250 U S P units of vitamin A and of not less than 25 U S P units of vitamin D

INTERNATIONAL VITAMIN CORPORATION

Cod Liver Oil 240 cc 480 cc and 720 cc bottles Each 1 Gm has a potency of not less than 2000 U S P units of vitamin A and of not less than 200 U S P units of vitamin D

THE MALTINE COMPANY

Maltine with Cod Liver Oil 480 cc and 960 cc bottles and 450 Gm and 3.84 liter jars. Each 100 cc contains cod liver oil 30 cc and maltine 70 cc. Each 1 Gm has a potency of not less than 250 U S P units of vitamin A and not less than 25 U S P units of vitamin D.

Maltine with Cod Liver Oil and Iron Iodide 480 cc bottle and 450 Gm and 3.84 liter jars. Maltine with cod liver oil to which has been added 0.44 Gm of ferrous iodide per 100 cc (2 grains to each fluidounce). Each 1 Gm of the preparation has a potency of not less than 250 U S P units of vitamin A and of not less than 25 U S P units of vitamin D.

The maltine used in the foregoing products is a preparation essentially similar to extract of malt U S P but it contains 19 per cent of alcohol and is prepared from malted barley oats and wheat U S trademark 44566.

MEAD JOHNSON AND COMPANY

Cod Liver Oil 120 cc 240 cc and 480 cc bottles. Each 1 Gm has a potency of not less than 1800 U S P units of vitamin A and of not less than 25 U S P units of vitamin D.

Cod Liver Oil Flavored 120 cc 240 cc and 480 cc bottles. Cod liver oil to which has been added 0.12 per cent of a mixture of U S P essential oils as a flavoring agent.

Cod Liver Oil Fortified with Percomorph Liver Oil 480 cc. Consists of Mead's standardized cod liver oil with percomorph and other fish liver oils. Not less than 50 per cent of the vitamin content is derived from percomorph liver oil. Supplies not less than 6000 U S P units of vitamin A and 850 U S P units of vitamin D. Biologically assayed.

PARKE, DAVIS & COMPANY

Cod Liver Oil 120 cc 360 cc and 480 cc bottles. Each 1 Gm has a potency of not less than 2000 U S P units of vitamin A and of not less than 250 U S P units of vitamin D.

Soluble Gelatin Capsules Cod Liver Oil 0.65 cc and 1.3 cc.

THE E. L. PATCH COMPANY

Flavored Cod Liver Oil 120 cc 360 cc and 480 cc bottles. Cod liver oil to which has been added 0.5 per cent of essential oils as flavoring. Each 1 Gm has a potency of not less than 2000 U S P units of vitamin A and of not less than 200 U S P units of vitamin D.

E. R. SQUIBB & SONS

Cod Liver Oil 120 cc, 360 cc and 720 cc bottles Each 1 Gm has a potency of not less than 1800 U S P units of vitamin A and not less than 180 U S P units of vitamin D
U S patent 1 829 571 (Oct 27, 1931 expires 1948)

Mint-Flavored Cod Liver Oil 120 cc, 360 cc and 720 cc bottles Cod liver oil to which has been added 0.67 per cent of oil of spearmint as flavoring

TAILBY-NASON COMPANY

Palatable Cod Liver Oil 120 cc and 360 cc bottles Cod liver oil containing not over 0.5 per cent of essential oils as flavoring Each 1 Gm has a potency of not less than 1400 U S P units of vitamin A and of not less than 130 U S P units of vitamin D

COD LIVER OIL WITH VIOSTEROL—Viosterol dissolved in cod liver oil to adjust it to the potency of not less than 850 units (U S P) of vitamin A per Gm, 360 units (U S P) of vitamin D per Gm

Actions and Uses—See general article, Viosterol Cod liver oil with viosterol is proposed for use in conditions in which it is desired to supplement the administration of vitamin A with that of a relatively large amount of vitamin D

Dosage—For infants and young children 25 to 33 cc daily, for adults and in severe cases doses up to 7 cc or more are given

Preparation—

Cod liver oil with viosterol is prepared by addition of irradiated ergosterol to cod liver oil in such proportion that the finished product will have a potency of not less than 850 units (U S P) of vitamin A per Gm and not less than 360 units (U S P) of vitamin D per Gm

MEAD JOHNSON AND COMPANY

Cod Liver Oil with Viosterol 118 cc and 473 cc bottle Each 1 Gm has a potency of not less than 1800 U S P units of vitamin A and of not less than 400 U S P units of vitamin D

PARKE, DAVIS & COMPANY

Cod Liver Oil with Viosterol 90 cc and 480 cc bottles Each 1 Gm has a potency of not less than 2000 U S P units of vitamin A and of not less than 400 U S P units of vitamin D

L. R. Squinn & Sons

Cod Liver Oil with Viosterol 99 cc and 450 cc bottles. Each 1 Gm. has a potency of not less than 200 U. S. P. units of vitamin A and of not less than 440 U. S. P. units of vitamin D.

Cod Liver Oil with Viosterol, Mint Flavored 99 cc and 450 cc bottles. Cod liver oil with viosterol to which has been added 0.67 per cent of oil of spearmint as flavoring.

COD LIVER OIL CONCENTRATE (LIQUID)

A concentrate of the non-saponifiable fraction of cod liver oil dissolved in cod liver oil or in neutral vegetable oil. Preparations of cod liver oil concentrate having a vitamin A potency of not less than 5000 and not more than 6500 units per gram and a vitamin D potency of not less than 500 and not more than 650 units per gram will be considered for acceptance.

Identification and Test—Cod liver oil concentrate (liquid) possesses properties similar to those of cod liver oil so far as these depend on the vitamin content of the latter.

Dose—Presbylactic. For liquid (1) 12 drops daily for children 1 or 2 capsules daily.

Cod liver oil concentrate is made under U. S. patent 1,127,971 (O. P. 1934) by L. R. Squinn & Sons, Inc., 1414 Broadway, New York 10, N. Y.

CRINABOL COMPANY, INC.

Cod Liver Oil Concentrate 10 cc, 1 fl. oz., 2 fl. oz. and 4 fl. oz. dispenser designed to deliver approximately 1 drop per drop. An extract of the non-saponifiable fraction of cod liver oil in mineral oil to which has been added vitamin D (3 in 1000) and oil of saffron 2 per cent. Each 1 Gm. of the concentrate has a potency of not less than 1000 U. S. P. units of vitamin A and of not less than 100 U. S. P. units of vitamin D.

U. S. Patents 2,411,111

INTERNATIONAL VITAMIN CORPORATION

Concentrate of Vitamins A and D from Cod Liver Oil in Vegetable Oil 1 cc, 1 fl. oz., 2 fl. oz. Each 1 Gm. has a potency of not less than 1000 U. S. P. units of vitamin A and of not less than 100 U. S. P. units of vitamin D.

Concentrate of Vitamins A and D from Cod Liver Oil in Vegetable Oil 1 cc, 1 fl. oz., 2 fl. oz. Each 1 Gm. has a potency of not less than 1000 U. S. P. units of vitamin A and of not less than 100 U. S. P. units of vitamin D.

Capsules Concentrate of Vitamins A and D from Cod Liver Oil in Vegetable Oil 1 cc, 1 fl. oz., 2 fl. oz. Each 1 Gm. has a potency of not less than 1000 U. S. P. units of vitamin A and of not less than 100 U. S. P. units of vitamin D.

WHITE LABORATORIES, INC

Cod Liver Oil Concentrate Liquid bulk A cod liver oil concentrate dissolved in cod liver oil having a potency of not less than 55 000 U S P units of vitamin A and of not less than 5 500 U S P units of vitamin D per gram

Cod Liver Oil Concentrate Capsules 0.195 cc Each capsule has a potency of not less than 5 000 U S P units of vitamin A and of not less than 500 U S P units of vitamin D

Cod Liver Oil Concentrate Liquid 6 cc 30 cc and 60 cc vials packaged with a dropper designed to supply in each 2 drops (0.062 cc) a potency of not less than 3 120 U S P units of vitamin A and of not less than 312 U S P units of vitamin D

WYETH, INCORPORATED

Carotene with Vitamin D Concentrate in Oil (See under Carotene)

COD LIVER OIL CONCENTRATE TABLETS—Cod liver oil in the form of tablets having a potency of not less than 3 120 U S P units of vitamin A and of not less than 312 U S P units of vitamin D

Actions and Uses—Cod Liver Oil Concentrate Tablets possess properties similar to cod liver oil so far as these depend on the fat soluble vitamin content of the latter

Dosage—Two to six tablets daily

INTERNATIONAL VITAMIN CORPORATION

Tablets Concentrate of Vitamins A and D from Cod Liver Oil Each tablet has a potency of not less than 3 150 U S P units of vitamin A and of not less than 315 U S P units of vitamin D

WHITE LABORATORIES, INC

Tablets Cod Liver Oil Concentrate Each tablet has a potency of not less than 3 120 U S P units of vitamin A and of not less than 312 U S P units of vitamin D

HALIBUT LIVER OIL—The fixed oil obtained from the fresh or suitably preserved livers of *Hippoglossus hippoglossus* Linné (Fam. *Pleuronectidae*) Halibut Liver Oil contains in each Gm not less than 60 000 U S P units of vitamin A and not less than 600 U S P units of vitamin D

The vitamin A potency and vitamin D potency of Halibut Liver Oil when designated on the label shall be expressed in United States Pharmacopeia Units per Gm of oil and may be referred to as U S P Units

Halibut Liver Oil may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in this Pharmacopeia 'U S P'

For description and standards see the U S Pharmacopeia under Halibut Liver Oil and Halibut Liver Oil Capsules

Actions and Uses—Halibut Liver Oil is used mainly as a source of vitamin A. See general article on Vitamin A.

Dosage—For infants 6 to 10 drops (25 to 35 minims) daily, for premature and rapidly growing infants, 15 drops (5.25 minims daily). For severe vitamin deficiencies 20 drops (7 minims) or more may be given at the discretion of the physician. The accepted preparations are marketed with an accompanying dropper designed to deliver a certain number of drops to the minim.

ABBOTT LABORATORIES

Haliver Oil, Plain 10 cc and 50 cc bottles. Each 1 Gm has a potency of not less than 60,000 U S P units of vitamin A and not less than 600 U S P units of vitamin D.

Haliver Oil Plain Capsules 0.095 cc. Each capsule has a potency of not less than 5,000 U S P units of vitamin A and not less than 50 U S P units of vitamin D.

U S patent No. 2,136,481 (Nov. 15, 1938 exp. res. 1955). Haliver is registered as trademark No. 294,697.

INTERNATIONAL VITAMIN CORPORATION

Halibut Liver Oil, Plain 11 cc and 60 cc bottles. Each 1 Gm has a potency of not less than 59,000 U S P units of vitamin A and of approximately 1,000 U S P units of vitamin D.

Capsules Halibut Liver Oil, Plain 0.195 cc. Each capsule has a potency of not less than 10,000 U S P units of vitamin A and of not less than 170 U S P units of vitamin D.

MCKESSON & ROBBINS, INC.

Halibut Liver Oil Plain 11 cc vials. Each 1 Gm has a potency of not less than 60,000 U S P units of vitamin A and of approximately 1,000 U S P units of vitamin D.

Capsules Halibut Liver Oil Plain 0.098 cc. Each capsule has a potency of not less than 5,000 U S P units of vitamin A and of not less than 85 U S P units of vitamin D.

MEAD JOHNSON AND COMPANY

Halibut Liver Oil 10 cc and 50 cc bottles. Each 1 Gm has a potency of not less than 60,000 U S P units of vitamin A and of approximately 800 U S P units of vitamin D.

PARKE DAVIS & COMPANY

Haliver Oil Plain 10 cc and 50 cc bottles Each 1 Gm has a potency of not less than 60 000 U S P units of vitamin A and of approximately 1 000 U S P units of vitamin D

Soluble Gelatine Capsules Haliver Oil, Plain 0.195 cc Each capsule contains haliver oil plain 3 minims with sufficient cod liver oil to fill the capsule

No U S patent Halver is registered as trademark no 294 692

E. R. SQUIBB & SONS

Soluble Gelatine Capsules Halibut Liver Oil Plain 0.098 cc Each capsule contains approximately 5 drops or 1 cc halibut liver oil plain which supplies 5 000 U S P units of vitamin A and 85 U S P units of vitamin D

THE UPJOHN COMPANY

Capsules Halibut Liver Oil 0.2 cc Each capsule has a potency of not less than 10 000 U S P units of vitamin A and not less than 170 U S P units of vitamin D

COD AND HALIBUT LIVER OIL—A blend of cod and halibut liver oils adjusted to a potency of not less than 3 600 nor more than 5 000 U S P units of vitamin A per gram and of not less than 360 nor more than 500 U S P units of vitamin D per gram

Actions and Uses—Cod and Halibut Liver Oil is used mainly as a source of vitamin A

Dosage—2 cc supplies the average prophylactic dose of natural vitamins A and D

HALIBUT LIVER OIL WITH VIOSTEROL—Halibut liver oil to which has been added sufficient viosterol (activated ergosterol) to assure a potency of not less than 10 000 U S P units of vitamin D per gram

Actions and Uses—The same as those for cod liver oil (See general article Vitamins A and D preparations)

Dosage—For infants 8 to 10 drops (about 0.6 cc) daily for premature and rapidly growing infants 15 drops (about 0.3 cc) daily for older children 15 to 20 drops (0.3 to 0.42 cc) daily for adults especially nursing and expectant mothers 20 drops (about 0.42 cc) or more daily The marketed preparation is accompanied by a special dropper designed to deliver a certain number of drops to the minim

ABBOTT LABORATORIES

Haliver Oil with Viosterol 5 cc 20 cc and 50 cc bottles

Soluble Gelatin Capsules Haliver Oil with Viosterol
0.09 cc Each capsule supplies 5000 U S P units of vitamin A and 1000 U S P units of vitamin D

INTERNATIONAL VITAMIN CORPORATION

Halibut Liver Oil with Viosterol in Oil 10 cc and 60 cc bottles

Soluble Gelatin Capsules Halibut Liver Oil with Viosterol in Oil 0.195 cc Each capsule supplies 5000 U S P units of vitamin A and 1700 U S P units of vitamin D

MCKESSON & ROBBINS, INC

Halibut Liver Oil with Viosterol in Oil 6 cc and 60 cc bottles

Soluble Gelatin Capsules Halibut Liver Oil with Viosterol in Oil 0.195 cc Each capsule supplies 8500 U S P units of vitamin A and 1700 U S P units of vitamin D

MEAD JOHNSON AND COMPANY

Viosterol in Halibut Liver Oil 10 cc and 50 cc bottles

PARKE DAVIS & COMPANY

Haliver Oil with Viosterol 5 cc 20 cc and 50 cc bottles

Soluble Gelatin Capsules Haliver Oil with Viosterol
Each capsule supplies 5000 U S P units of vitamin A and 1000 U S P units of vitamin D

E. R. SQUIBB & SONS

Soluble Gelatine Capsules Halibut Liver Oil with Viosterol 0.098 cc Each capsule supplies 5000 U S P units of vitamin A and 1000 U S P units of vitamin D

PERCOMORPH LIVER OIL — *Oleum Percomorphum* — A mixture containing the fixed oils obtained from the fresh livers of the percomorph fishes principally *Xiphias gladius*, *Pneumatophorus d'ego*, *Thunnus thynnus* and *Stereolepis gigas* —sard scom morio *Roccus lineatus*, *Cynoscion nobilis*, *Eriscion macdonaldi*, *Epinephelus analogus*, *Stereolepis ishmagi* and *Sphyræna argentea* containing not more than 50 per cent of other fish

Transfer 2 Gm of shark liver oil, accurately weighed, to an Erlenmeyer flask and dissolve in 20 cc of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth normal sodium hydroxide, using five drops of phenolphthalein T. S. as indicator, and titrate with tenth normal sodium hydroxide to the production of a pink color which persists for fifteen seconds, not more than 1 cc of tenth normal sodium hydroxide is required (*free acid*). The amount of unsaponifiable matter as determined by the method of the U S P is not less than 30 per cent nor more than 60 per cent. The saponification value as determined by the method of the U S P is not less than 170 nor more than 187. The iodine value as determined by the method of the U S P on from 0.18 to 0.20 Gm of sample, accurately weighed, is not less than 125 nor more than 145.

SHARK INDUSTRIES, INC.

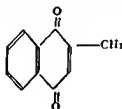
Shark Liver Oil: 30 and 120 cc bottles

Capsules Shark Liver Oil: 0.3 cc Each capsule supplies not less than 5,000 U S P units of vitamin A

Vitamin K Preparations

For allowable claims see preceding article, Vitamin K

MENADIONE — 2-Methyl-1,4-Naphthoquinone — Thiloquinone — 'When dried over sulfuric acid in a vacuum desiccator for 4 hours, contains not less than 98.5 per cent of $C_{11}H_8O_2$.' U S P Menadione has the following structural formula



It may be prepared by oxidizing 2-methylnaphthalene with chromic acid

For description and standards see the U S Pharmacopeia under Menadione and Menadione Tablets

The acceptance of tablets menadione is limited to 1 and 2 mg of menadione per tablet, the acceptance of capsules menadione is limited to 1 and 2 mg of menadione per capsule, and the acceptance of ampul solution for parenteral use is limited to 1 and 2 mg of menadione per cc

Actions and Uses—A synthetic naphthoquinone derivative having physiologic properties of vitamin K. See the general article, Vitamin K

Dosage—From 1 to 2 mg daily. The dose should not exceed 2 mg a day and should not be continued at 2 mg a day for a

period exceeding four weeks. When the preparation is given orally bile salts should be administered with menadione in cases of prothrombin deficiency due to bile obstruction.

GEORGE A. BREON & COMPANY, INC.

Tablets Menadione 2 mg

INDO PRODUCTS, INC.

Tablets Menadione 1 mg and 2 mg

Solution Menadione (in corn oil) 2 mg per 2 cc 2 cc ampuls Each cubic centimeter contains 1 mg menadione

LAKESIDE LABORATORIES, INC.

Menadione (in sesame oil) 2 mg 1 cc ampuls Contains 0.5 per cent of chlorobutanol as preservative

Capsules Menadione (in corn oil) 2 mg

MCNEIL LABORATORIES

Capsules Menadione (in corn oil) 2 mg

MEAD JOHNSON & COMPANY

Capsules Menadione 1 mg

MERCK & CO., INC.

Menadione (*Powder*)

SCHIEFFELIN & CO.

Tablets Menadione 1 mg

Menadione (in sesame oil) 1 mg per cc 10 cc vials Each cubic centimeter contains 1 mg menadione

SHARP & DOHME, INC. GREENSBORO, PA.

Tablets Menadione 1 mg

Solution Menadione (in peanut oil) 2 mg per cc 1 cc ampuls

SMITH DORSEY COMPANY

Tablets Menadione 1 mg

E. R. SQUIBB & SONS

Thyloquinone (in corn oil) (Intramuscular), 2 mg per cc 1 cc ampuls Each cubic centimeter contains 2 mg of thyloquinone

liver oil It is biologically assayed to have a potency of not less than 60,000 units of vitamin A (U S P) per gram and of not less than 8 500 units of vitamin D (U S P) per gram

Actions and Uses—Same as those of cod liver oil See general article, Vitamins A and D Preparations

Dosage—Prophylactic, for normal infants, 10 drops daily, curative and in severe conditions, to 20 drops daily The product is marketed with a dropper designed to deliver 44 drops to the cc

Tests and Standards—

Percomorph liver oil, 50% in fish liver oil is a yellow to brownish yellow oily liquid It has a slightly fishy but not rancid odor and a fishy taste It is slightly soluble in alcohol but is soluble in ether, chloroform benzene carbon disulfide and ethyl acetate The specific gravity is from 0.922 to 0.930 at 25 C The refractive index is from 1.480 to 1.485 at 20 C

A solution of one drop of the oil in 1 cc. of chloroform when shaken with one drop of sulfuric acid acquires a blue color, changing to violet dark green and finally brown. Treat 5 cc. of oil with 5 cc of benzene and centrifuge for twenty five minutes at 25 C., no precipitate forms and a clear solution remains

Fill a tall cylindric standard oil sample bottle of about 120 cc capacity with percomorph liver oil 50% in fish liver oil at a temperature between 23 and 28 C stopper and immerse the bottle in a mixture of ice and distilled water for five hours the oil remains fluid and forms no deposit

Dissolve 2 Gm of percomorph liver oil 50% in fish liver oil in 20 cc of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth normal sodium hydroxide using 5 drops of phenolphthalein T S as indicator, and titrate with tenth normal sodium hydroxide to the production of a pink color which persists for fifteen seconds not more than 1 cc. of tenth normal sodium hydroxide is required (*free acid*) The amount of unsaponifiable matter as determined by the method of U S P is not less than 3.5 per cent nor more than 7 per cent it is semisolid in appearance The saponification value as determined by the method of U S P is not less than 174 and not more than 186 The iodine value as determined by the method of U S P on 0.18 to 0.20 Gm of sample accurately weighed is not less than 145 and not more than 180

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| morph | of percomorph liver oil 50 |
| per cc | the following constants as |
| determin | cific gravity from 0.924 to |
| 0.930 a | 484 to 1.490 at 20 C free |
| acid in 2 Gm. | equivalent to not more than 1 cc of tenth normal |
| sodium hydroxide, | unsaponifiable matter not less than 7 nor more |
| than 13 per cent (semi solid in appearance) | saponification value not |
| less than 168 nor more than 182 | iodine value not less than 145 nor |
| more than 180 | |

AMERICAN PHARMACEUTICAL CO., INC

Codanol Brand Percomorph Liver Oil 50% with Vioosterol 10 cc and 50 cc. A source of vitamin A and D in which not less than 50 per cent of the vitamin content is derived from the liver oils of percomorph fishes with viosterol added Each gram contains not less than 60 000 U S P units of vitamin A and 8 500 U S P units of vitamin D

FLINT, EATON & COMPANY

Oleum Percomorphum: 8 cc bottle

MEAD JOHNSON AND COMPANY

Oleum Percomorphum with Other Fish-Liver Oils and Viosterol: A blend of liver oils of percomorph fishes, viosterol and other fish liver oils. A source of vitamin A and D in which not less than 50 per cent of the vitamin content is derived from the livers of percomorph fishes. Each gram contains not less than 60,000 U S P units of vitamin A and 8,500 U S P units of vitamin D.

**Oleum Percomorphum with Other Fish-Liver Oils and
Vitaminol: 50 cc bottles**

Capsules Oleum Percomorphum with Other Fish-Liver Oils and Viosterol; Each capsule contains 83 mg of oleum percomorphum with other fish liver oils and viosterol and supplies a potency of 5000 U S P units of vitamin A and 700 U S. P units of vitamin D.

SHARK LIVER OIL.—The oil extracted from the livers of the shark, mainly of the variety *Hypoprion brevirostris* (lemon), but any or all of the following varieties may be included *Odontaspis littoralis* (sand), *Isurus punctatus* (mackerel), *Triakis semifasciatus* (leopard), *Sphyrna zygaena* (hammerhead), *Carcharias obscurus* (dusky) *Ginglymostoma cirratum* (nurse), *Carcharias milberti* (white) and *Carcharias limbatus* of not and of the last

Actions and Uses—See the general article Vitamins A and D
Preparations

Dosage—One capsule, or about 0.52 cc., daily

Tests and Standards—

Shark liver oil is an amber to brown oily liquid possessing a fishy odor and taste. It is insoluble in water, slightly soluble in alcohol and soluble in chloroform, ether, benzene, ethyl acetate and carbon disulfide. The specific gravity is from 0.917 to 0.923 at 25 C. The refractive index is from 1.475 to 1.480 at 20 C.

A solution of one drop of the oil in 1 cc of chloroform when shaken with one drop of sulfuric acid, acquires a light violet color changing to purple and finally brown or blue. Transfer 5 cc of oil to a centrifuge tub and add 5 cc of benzene, centrifugate for twenty five minutes at 25 C., no precipitate forms and a clear solution remains.

Fill a tall cylindrical, standard oil sample bottle of about 120 cc capacity with shark liver oil and immerse in a water bath at about 10 C; the oil becomes turbid at about 15 C but fluid and clear when the bath is warmed to 45 C.

Transfer 2 Gm of shark liver oil, accurately weighed, to an Erlenmeyer flask and dissolve in 20 cc of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth normal sodium hydroxide, using five drops of phenolphthalein T S as indicator, and titrate with tenth normal sodium hydroxide to the production of a pink color which persists for fifteen seconds, not more than 1 cc of tenth normal sodium hydroxide is required (*free acid*). The amount of unsaponifiable matter as determined by the method of the U S P is not less than 30 per cent nor more than 60 per cent. The saponification value as determined by the method of the U S P is not less than 170 nor more than 187. The iodine value as determined by the method of the U S P on from 0.18 to 0.20 Gm of sample, accurately weighed, is not less than 125 nor more than 145.

SHARK INDUSTRIES, INC.

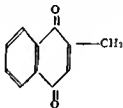
Shark Liver Oil: 30 and 120 cc bottles

Capsules Shark Liver Oil: 0.3 cc Each capsule supplies not less than 5,000 U S P units of vitamin A

Vitamin K Preparations

For allowable claims see preceding article, Vitamin K

MENADIONE. — 2-Methyl 1,4-Naphthoquinone — Thyloquinone — When dried over sulfuric acid in a vacuum desiccator for 4 hours, contains not less than 98.5 per cent of $C_{11}H_8O_2$. U S P Menadione has the following structural formula



It may be prepared by oxidizing 2-methylnaphthalene with chromic acid

For description and standards see the U S Pharmacopoeia under Menadione and Menadione Tablets

The acceptance of tablets menadione is limited to 1 and 2 mg of menadione per tablet, the acceptance of capsules menadione is limited to 1 and 2 mg of menadione per capsule, and the acceptance of ampul solution for parenteral use is limited to 1 and 2 mg of menadione per cc

Actions and Uses.—A synthetic naphthoquinone derivative having physiologic properties of vitamin K. See the general article, Vitamin K

Dosage.—From 1 to 2 mg daily. The dose should not exceed 2 mg a day and should not be continued at 2 mg a day for a

period exceeding four weeks. When the preparation is given orally, bile salts should be administered with menadione in cases of prothrombin deficiency due to bile obstruction.

GEORGE A. BREON & COMPANY, INC.

Tablets Menadione 2 mg

LINDO PRODUCTS, INC.

Tablets Menadione 1 mg and 2 mg

Solution Menadione (in corn oil) 2 mg per 2 cc 2 cc ampuls. Each cubic centimeter contains 1 mg menadione.

LAKESIDE LABORATORIES, INC.

Menadione (in sesame oil) 2 mg 1 cc ampuls. Contains 0.5 per cent of chlorobutanol as preservative.

Capsules Menadione (in corn oil) 2 mg

MCKEN LABORATORIES

Capsules Menadione (in corn oil) 2 mg

MEAD JOHNSON & COMPANY

Capsules Menadione 1 mg

MERCK & CO., INC.

Menadione (Powder)

SCHIEFFELIN & CO.

Tablets Menadione 1 mg

Menadione (in sesame oil) 1 mg per cc 10 cc vials. Each cubic centimeter contains 1 mg menadione.

SHARP & DOHME INC. GREENGLASS, PA.

Tablets Menadione 1 mg

Solution Menadione (in peanut oil) 2 mg per cc 1 cc ampuls.

SMITH DORSEY COMPANY

Tablets Menadione 1 mg

E. R. SQUIBB & SONS

Thyloquinone (in corn oil) (Intramuscular), 2 mg per cc 1 cc ampuls. Each cubic centimeter contains 2 mg of thyloquinone.

readily oxidizable in air. Add one drop of vitamin K₁ to a mixture of 1 cc of concentrated ammonium hydroxide and 1 cc of ethanol and then add one drop of ethylcyanoacetate; no purple color is produced (absence of menadione). A solution of one part vitamin K₁ and 20 parts ethanol is neutral to litmus.

MERCK & Co., Inc.

Vitamin K₁ 1 Gm 5 Gm and 25 Gm ampuls

Mixed Vitamin Preparations

HEXAVITAMIN TABLETS — "Hexavitamin Tablets contain in each tablet not less than 2500 U S P units of vitamin A from natural (animal) sources 200 U S P units of vitamin D from natural (animal) sources or as activated ergosterol or activated 7-dehydrocholesterol 37 mg of ascorbic acid, 1 mg of thiamine hydrochloride, 15 mg of riboflavin and 10 mg of nicotinamide" — U S P

For description and standards see the U S Pharmacopeia XII First Bound Supplement under Tabellae Hexavitaminarum

Actions Uses and Dosage — For prophylaxis and treatment of conditions arising from deficiency of vitamins A and D and ascorbic acid, thiamine, riboflavin and nicotinic acid. See articles on the various vitamins concerned.

INTERNATIONAL VITAMIN CORPORATION

Tablets Hexavitamin Each tablet contains 2,500 U S P units of vitamin A, 200 U S P units of vitamin D 37 mg of ascorbic acid, 1 mg of thiamine hydrochloride 15 mg of riboflavin and 10 mg of niacin amide

COD LIVER OIL WITH VIOSTEROL (See under Vitamins A and D Preparations)

PERCOMORPH LIVER OIL (See under Vitamin A and D Preparations)

TRIASYN B (See under Mixed Vitamin B Components)



BIBLIOGRAPHIC INDEX TO MEDICINAL
ARTICLES NOT INCLUDED IN NNR

This cumulative index is intended to aid the reader in determining the status of articles which do not stand accepted by the Council and to supply him with sources of useful information on such articles. It provides a ready reference to reports of the Council on Pharmacy and Chemistry explaining the rejection of an article or the omission from New and Non-official Drugs, ² ³ ⁴ ⁵ ⁶ ⁷ ⁸ ⁹ ¹⁰ ¹¹ ¹² ¹³ ¹⁴ ¹⁵ ¹⁶ ¹⁷ ¹⁸ ¹⁹ ²⁰ ²¹ ²² ²³ ²⁴ ²⁵ ²⁶ ²⁷ ²⁸ ²⁹ ³⁰ ³¹ ³² ³³ ³⁴ ³⁵ ³⁶ ³⁷ ³⁸ ³⁹ ⁴⁰ ⁴¹ ⁴² ⁴³ ⁴⁴ ⁴⁵ ⁴⁶ ⁴⁷ ⁴⁸ ⁴⁹ ⁵⁰ ⁵¹ ⁵² ⁵³ ⁵⁴ ⁵⁵ ⁵⁶ ⁵⁷ ⁵⁸ ⁵⁹ ⁶⁰ ⁶¹ ⁶² ⁶³ ⁶⁴ ⁶⁵ ⁶⁶ ⁶⁷ ⁶⁸ ⁶⁹ ⁷⁰ ⁷¹ ⁷² ⁷³ ⁷⁴ ⁷⁵ ⁷⁶ ⁷⁷ ⁷⁸ ⁷⁹ ⁸⁰ ⁸¹ ⁸² ⁸³ ⁸⁴ ⁸⁵ ⁸⁶ ⁸⁷ ⁸⁸ ⁸⁹ ⁹⁰ ⁹¹ ⁹² ⁹³ ⁹⁴ ⁹⁵ ⁹⁶ ⁹⁷ ⁹⁸ ⁹⁹ ¹⁰⁰ ¹⁰¹ ¹⁰² ¹⁰³ ¹⁰⁴ ¹⁰⁵ ¹⁰⁶ ¹⁰⁷ ¹⁰⁸ ¹⁰⁹ ¹¹⁰ ¹¹¹ ¹¹² ¹¹³ ¹¹⁴ ¹¹⁵ ¹¹⁶ ¹¹⁷ ¹¹⁸ ¹¹⁹ ¹²⁰ ¹²¹ ¹²² ¹²³ ¹²⁴ ¹²⁵ ¹²⁶ ¹²⁷ ¹²⁸ ¹²⁹ ¹³⁰ ¹³¹ ¹³² ¹³³ ¹³⁴ ¹³⁵ ¹³⁶ ¹³⁷ ¹³⁸ ¹³⁹ ¹⁴⁰ ¹⁴¹ ¹⁴² ¹⁴³ ¹⁴⁴ ¹⁴⁵ ¹⁴⁶ ¹⁴⁷ ¹⁴⁸ ¹⁴⁹ ¹⁵⁰ ¹⁵¹ ¹⁵² ¹⁵³ ¹⁵⁴ ¹⁵⁵ ¹⁵⁶ ¹⁵⁷ ¹⁵⁸ ¹⁵⁹ ¹⁶⁰ ¹⁶¹ ¹⁶² ¹⁶³ ¹⁶⁴ ¹⁶⁵ ¹⁶⁶ ¹⁶⁷ ¹⁶⁸ ¹⁶⁹ ¹⁷⁰ ¹⁷¹ ¹⁷² ¹⁷³ ¹⁷⁴ ¹⁷⁵ ¹⁷⁶ ¹⁷⁷ ¹⁷⁸ ¹⁷⁹ ¹⁸⁰ ¹⁸¹ ¹⁸² ¹⁸³ ¹⁸⁴ ¹⁸⁵ ¹⁸⁶ ¹⁸⁷ ¹⁸⁸ ¹⁸⁹ ¹⁹⁰ ¹⁹¹ ¹⁹² ¹⁹³ ¹⁹⁴ ¹⁹⁵ ¹⁹⁶ ¹⁹⁷ ¹⁹⁸ ¹⁹⁹ ²⁰⁰ ²⁰¹ ²⁰² ²⁰³ ²⁰⁴ ²⁰⁵ ²⁰⁶ ²⁰⁷ ²⁰⁸ ²⁰⁹ ²¹⁰ ²¹¹ ²¹² ²¹³ ²¹⁴ ²¹⁵ ²¹⁶ ²¹⁷ ²¹⁸ ²¹⁹ ²²⁰ ²²¹ ²²² ²²³ ²²⁴ ²²⁵ ²²⁶ ²²⁷ ²²⁸ ²²⁹ ²³⁰ ²³¹ ²³² ²³³ ²³⁴ ²³⁵ ²³⁶ ²³⁷ ²³⁸ ²³⁹ ²⁴⁰ ²⁴¹ ²⁴² ²⁴³ ²⁴⁴ ²⁴⁵ ²⁴⁶ ²⁴⁷ ²⁴⁸ ²⁴⁹ ²⁵⁰ ²⁵¹ ²⁵² ²⁵³ ²⁵⁴ ²⁵⁵ ²⁵⁶ ²⁵⁷ ²⁵⁸ ²⁵⁹ ²⁶⁰ ²⁶¹ ²⁶² ²⁶³ ²⁶⁴ ²⁶⁵ ²⁶⁶ ²⁶⁷ ²⁶⁸ ²⁶⁹ ²⁷⁰ ²⁷¹ ²⁷² ²⁷³ ²⁷⁴ ²⁷⁵ ²⁷⁶ ²⁷⁷ ²⁷⁸ ²⁷⁹ ²⁸⁰ ²⁸¹ ²⁸² ²⁸³ ²⁸⁴ ²⁸⁵ ²⁸⁶ ²⁸⁷ ²⁸⁸ ²⁸⁹ ²⁹⁰ ²⁹¹ ²⁹² ²⁹³ ²⁹⁴ ²⁹⁵ ²⁹⁶ ²⁹⁷ ²⁹⁸ ²⁹⁹ ³⁰⁰ ³⁰¹ ³⁰² ³⁰³ ³⁰⁴ ³⁰⁵ ³⁰⁶ ³⁰⁷ ³⁰⁸ ³⁰⁹ ³¹⁰ ³¹¹ ³¹² ³¹³ ³¹⁴ ³¹⁵ ³¹⁶ ³¹⁷ ³¹⁸ ³¹⁹ ³²⁰ ³²¹ ³²² ³²³ ³²⁴ ³²⁵ ³²⁶ ³²⁷ ³²⁸ ³²⁹ ³³⁰ ³³¹ ³³² ³³³ ³³⁴ ³³⁵ ³³⁶ ³³⁷ ³³⁸ ³³⁹ ³⁴⁰ ³⁴¹ ³⁴² ³⁴³ ³⁴⁴ ³⁴⁵ ³⁴⁶ ³⁴⁷ ³⁴⁸ ³⁴⁹ ³⁵⁰ ³⁵¹ ³⁵² ³⁵³ ³⁵⁴ ³⁵⁵ ³⁵⁶ ³⁵⁷ ³⁵⁸ ³⁵⁹ ³⁶⁰ ³⁶¹ ³⁶² ³⁶³ ³⁶⁴ ³⁶⁵ ³⁶⁶ ³⁶⁷ ³⁶⁸ ³⁶⁹ ³⁷⁰ ³⁷¹ ³⁷² ³⁷³ ³⁷⁴ ³⁷⁵ ³⁷⁶ ³⁷⁷ ³⁷⁸ ³⁷⁹ ³⁸⁰ ³⁸¹ ³⁸² ³⁸³ ³⁸⁴ ³⁸⁵ ³⁸⁶ ³⁸⁷ ³⁸⁸ ³⁸⁹ ³⁹⁰ ³⁹¹ ³⁹² ³⁹³ ³⁹⁴ ³⁹⁵ ³⁹⁶ ³⁹⁷ ³⁹⁸ ³⁹⁹ ⁴⁰⁰ ⁴⁰¹ ⁴⁰² ⁴⁰³ ⁴⁰⁴ ⁴⁰⁵ ⁴⁰⁶ ⁴⁰⁷ ⁴⁰⁸ ⁴⁰⁹ ⁴¹⁰ ⁴¹¹ ⁴¹² ⁴¹³ ⁴¹⁴ ⁴¹⁵ ⁴¹⁶ ⁴¹⁷ ⁴¹⁸ ⁴¹⁹ ⁴²⁰ ⁴²¹ ⁴²² ⁴²³ ⁴²⁴ ⁴²⁵ ⁴²⁶ ⁴²⁷ ⁴²⁸ ⁴²⁹ ⁴³⁰ ⁴³¹ ⁴³² ⁴³³ ⁴³⁴ ⁴³⁵ ⁴³⁶ ⁴³⁷ ⁴³⁸ ⁴³⁹ ⁴⁴⁰ ⁴⁴¹ ⁴⁴² ⁴⁴³ ⁴⁴⁴ ⁴⁴⁵ ⁴⁴⁶ ⁴⁴⁷ ⁴⁴⁸ ⁴⁴⁹ ⁴⁵⁰ ⁴⁵¹ ⁴⁵² ⁴⁵³ ⁴⁵⁴ ⁴⁵⁵ ⁴⁵⁶ ⁴⁵⁷ ⁴⁵⁸ ⁴⁵⁹ ⁴⁶⁰

agents not accepted for N N R. References to preliminary reports of the Council which as a rule deal with new articles possessing potential acceptability for N N R are not included. Information on these and on any other article or subject included in the Council's extensive files may be obtained by addressing an inquiry to the Secretary of the Council.

The references given below include first the date of original publication of the article in *The Journal A M A* if it appeared there, and second for the benefit of those that do not have access to files of *The Journal* the place where a discussion of the article may be found in other publications. Reports of the Council on Pharmacy and Chemistry, 'Propaganda for Reform' and 'Reports of the A M A Chemical Laboratory' Council reports include reports on articles that have been considered by the Council either at the request of the manufacturers or on the Council's own initiative. The names of the manufacturers (or their agents) follow the names of the preparations except in those instances in which a drug is discussed in general, without reference to the product of any particular manufacturer.

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- Influenza Vaccine No 39 (G H Sherman) Influenza Serobacterin Mixed Mulford Micrococcus Catarrhal Combined Vaccine (Abbott Laboratories) Mixed Staphylococcus Aene Vaccine Mixed Vaccine No 40 Sherman's Pertussis Bacterin Mixed (H K Mulford) Pertussis Combined Bacterin (Abbott Laboratories), Pertussis Serobacterin Mixed Mulford Pneumo Mixed Vaccine No 6 (G H Sherman) Staph Aene Vaccine (Cutler Laboratory) Streptococcus Rheumaticus Combined Bacterin (Abbott Laboratories) Streptococcus Viridans Combined Bacterin (Abbott Laboratories) Strepto Staph Vaccine No 10 (G H Sherman) Whooping Cough Mixed Vaccine (G H Sherman)
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- BILHUBER KNOLL CORP.**, Crane St., Orange, N. J.—Afenil, 479; Bromural, 499; Dilaudid Hydrochloride, 503; Furesol pro Capillis, 168; Lenigallol Zinc, 278; Metrazol, 347; Theocalcin, 394
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- BUFFINGTON'S INC.** 8 Sudbury St., Worcester, Mass.—Nikethamide, 350; Phenobarbital, 530; Sulfadiazine 184; Sulfathiazole, 202
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- CIBA**, N. J.—agnostic, pyridine.
- CLINADOL COMPANY, INC.**, 522 Fifth Ave., New York, N. Y.—Cod Liver Oil Concentrate, 643
- COLEMAN & BELL, THE, COMPANY INC.**, Norwood, Ohio—Gentian Violet Medicinal, 124
- COMMERCIAL SOLVENTS CORPORATION**, 17 East 42nd St., New York, N. Y.—Penicillin Calcium, 214; Penicillin Sodium, 214
- CONTINENTAL HOSPITAL SERVICE INC.**, 18636 Detroit Ave., (Lakewood) Cleveland 7, Ohio—Lactate Ringer's Solution, 493
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 Isophtalene Sodium 389, Kelene 101, Mandelic Acid 175,
 Methyl Bromide, 308, Methyl Chloride 311, Menadione 651,
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